REPORTING BIAS
AMONG RANDOMIZED CONTROLLED TRIALS FROM CHINA

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Abstract

Research Question

Reporting bias threatens the validity of evidence. This dissertation addressed three types of reporting bias, i.e., primary outcome switching, language bias, and duplicate publication bias among randomized controlled trials (RCTs) from mainland China.

Method

RCTs that evaluated the efficacy and/or safety of drug interventions and were conducted in mainland China between 2008 and 2014, were retrieved from trial registries, and their corresponding journal articles were identified from both English and Chinese bibliographic databases.

First, we evaluated the association between the findings of registered primary outcomes (positive vs. negative) and the switching of registered primary outcomes (registered primary outcomes switched to secondary outcomes in the journal articles vs. registered primary outcomes remained primary in the journal articles). Second, we evaluated the association between the finding of RCTs (positive vs. negative) and the language of corresponding journal articles published subsequently (English vs. Chinese). Third, we evaluated the association between the findings of RCTs (positive vs. negative) and the occurrence of subsequent duplicates.

Results

When RCTs were prospectively registered, the odds of switching primary outcomes with negative findings were 2.34 (95%CI: 1.03 to 5.33) times the odds of switching primary outcomes with positive findings. When RCTs were retrospectively registered before trial completion, the

odds of switching primary outcomes with negative findings were 9.69 (95%CI: 3.62 to 25.93) times the odds of switching primary outcomes with positive findings.

Among RCTs registered in bilingual registry, RCTs with positive findings were 3.92 (95%CI: 2.20-7.00) times more likely to be published in English than those with negative findings; among RCTs registered in English registries, RCTs with positive findings were 3.22 (95%CI: 1.34-7.78) times more likely to be published in English than those with negative findings.

When the main articles of RCTs were published in Chinese, those with positive findings were 2.48 (95%CI: 1.08 – 5.71) times more likely to have subsequent duplicates than those with negative findings.

Conclusion

We found evidence supporting the three types of reporting bias among RCTs from mainland China, which may threaten the validity of evidence synthesized by systematic reviews.

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Introduction

1. Proliferating RCTs from Mainland China

Mainland China has become the largest producer of scientific publications since 2016, surpassing the United States.[1] Meanwhile, the number of RCTs from mainland China has increased from 16,000 in 2006 to more than 44,000 in 2016 [YJ, Jun Liang, JW, et al, unpublished data, June 2020]. Owing to the language barrier, more than 90% of those RCTs are published in Chinese and only indexed in Chinese bibliographic databases.

2. Reporting Bias as A Threat to the Evidence

Findings of RCTs should be neutrally disseminated to the academic society. However, it was revealed that in the Western world investigators may selectively report or suppress findings of RCTs based on their nature and direction. For example, investigators may selectively report statistically significant (also referred to as 'positive') findings supporting the hypothesis of the study. Such selective reporting or suppressing of findings may introduce bias into evidence synthesis practice, i.e., reporting bias.[2]

For example, it is well established that clinical trials with positive findings are more likely to be published than those with negative findings, i.e., publication bias;[3,4] in non-English-speaking countries, clinical trials with positive findings are more likely to be published in English than those with negative findings, i.e., language bias;[5] clinical trials with positive findings are more likely to be published multiple times than those with negative findings, i.e., duplicate publication bias;[6,7] clinical trials with positive findings are more likely to be published in high impact journals than those with negative findings, i.e., location bias;[8] clinical trials with positive findings are more likely to be cited by subsequent studies than those (citation bias);[9] and clinical trials with

positive results are more likely to be published more rapidly than those with negative results, i.e., time lag bias.[10,11]In addition, in individual clinical trials, outcomes with positive findings are more likely to be published than those with negative findings.[12]

Besides the seven types of reporting bias defined in the Cochrane Handbook, we consider primary outcome switching as another type of reporting bias owing its similar mechanism of occurrence. Primary outcome switching is defined as the phenomenon that registered primary outcomes with negative findings are more likely to be downgraded to secondary outcomes in the subsequent publications than those with positive findings.[4] Switching primary outcomes based on the nature of findings may artificially amplify the probability of false positive findings, bias the interpretation of the overall result, and lead to adoption of new therapies with spurious benefits.[13-15]

Reporting bias overexposes positive findings to researchers who may subsequently overestimate treatment effects of health interventions in systematic reviews and clinical practice guidelines, eventually leading to suboptimal health care decisions detrimental to patients.

3. Trial Registries Can Be Used to Evaluate Reporting Bias

Trial registries are standardized and free-of-charge platforms that document key protocol information of clinical trials, such as participants, interventions, and outcomes.[16] All clinical trials, regardless of design and sponsorship, should be registered before recruitment starts.[17] Any subsequent change of clinical trial protocols should be documented as well.

Trial registries can help researchers reduce the impact of reporting bias by identifying all relevant clinical trials regardless of their publishing status.[18] Meanwhile, trial registries make it possible for researchers to trace and audit the change of clinical trial protocols over time.[19]

Trial registration has been widely supported by the academic community and the legal authorities. In 2004, the International Committee of Medical Journal Editors announced that they would not publish reports of clinical trials unless they had been appropriately registered.[17] The 28th China Food and Drug Administration (China FDA) Announcement in 2007 mandated pre-registration of clinical trials conducted in mainland China on the Drug Clinical Trial Registration Platform (DCTRP) before recruitment started.[20] These actions have substantially prompted registration of RCTs from mainland China.[21]

4. Research Gap of Previous Studies

Although there has been abundant literature on reporting bias regarding RCTs, very few have been dedicated to RCTs from mainland China, therefore little is known on whether reporting bias exists or to what extent among RCTs from mainland China. Owing to different linguistic systems, academic structures, legislations, and research cultures, it may not be valid to directly extrapolate the findings from the Western world to mainland China. Given the number of RCTs conducted in China of relevance globally, it is urgent to conduct research on the existence of reporting bias among RCTs from mainland China and estimate how much this bias may affect the current evidence synthesis practice.

We propose a retrospective cohort study to evaluate the existence of three types of reporting bias among RCTs from China: primary outcome switching, language bias, and duplicate publication bias. Primary outcome switching, i.e., registered primary outcomes with positive findings are more likely to be switched in the subsequent publications than those with negative findings, is not one of the seven types of reporting bias defined in the Cochrane Handbook.[17]

5. Study Aims

Aim 1. To assess the association between the switching of registered primary outcomes (registered primary outcomes switched to secondary outcomes in the published journal articles vs. registered primary outcomes that remained primary in the published journal articles) and the findings of the registered primary outcomes (positive vs. negative) among RCTs from mainland China. We will compare the primary outcomes from trial registries with the corresponding outcomes published in the journal articles.

Hypothesis: Registered primary outcomes with negative findings are more likely to be downgraded to secondary outcomes in the journal articles than those with positive findings.

Aim 2. Assess (1) the association between the findings of RCTs (positive vs. negative) and the language of corresponding journal articles published subsequently (English vs. Chinese) and (2) the association between the findings of RCTs (positive vs. negative) and the language of the bibliographic databases where the journal articles were indexed (English vs. Chinese) among RCTs from mainland China.

Hypothesis: (1) RCTs with positive findings are more likely to be published in English than those with negative findings; (2) RCTs with positive findings are more likely to be indexed in English bibliographic databases than those with negative findings.

Aim 3. Describe the patterns of duplicate publications and assess the association between the findings of RCTs (positive vs. negative) and the occurrence of subsequent duplicate publications (having vs. not having subsequent duplicate publications).

Hypothesis: RCTs with positive findings are more likely to have subsequent duplicate publications than those with negative findings.

6. Dissertation Data Source

All the data in this dissertation are collected from public-available sources. There is no need to request approval from the institutional review board.

RCTs from mainland China are retrieved from trial registries, including the primary registries recognized by the World Health Organizations and DCTRP sponsored by the China FDA.[22] The corresponding journal articles are identified from seven bibliographic databases, three English ones (PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL)); and four Chinese ones: the China National Knowledge Infrastructure (CNKI), SinoMed, the VIP information, and the Wanfang Data).[23]

7. Dissertation Structure

This dissertation has three chapters and a conclusion. Each chapter is formatted as a publishable manuscript. Chapter 1 assesses the switching of primary outcomes. Chapter 2 assesses language bias and indexing bias. Chapter 3 develops patterns of duplicates and assesses duplicate publication bias. The conclusion summarizes the findings and outlines next steps for this research.

Chapter 1

Association between Switching of Primary Outcomes and Reported Trial Findings

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Abstract

Importance Switching primary outcomes based on the findings may lead to biased interpretation of trial results and adoption of therapies with spurious benefits.

Objective To evaluate whether among randomized clinical trials (RCTs), registered primary outcomes with negative findings were more likely to be switched to secondary outcomes in the

published journal articles than those with positive findings, and whether this association was modified by the timing of registration.

Design Retrospective cohort study.

Settings Trial registries and bibliographic databases.

Participants RCTs sponsored by organizations located in mainland China conducted between 2008 and 2014. Eligible RCTs were retrieved from trial registries and the journal articles were identified from bibliographic databases until August 2019.

Exposure Findings of primary outcome (positive vs. negative).

Main Outcomes and Measures Registered primary outcome being switched to secondary outcome in the journal article. The timing of registration (prospective registration vs. retrospective registration before trial completion vs. retrospective registration after trial completion) was pre-specified as an effect-modifier.

Results Switching of primary outcomes occurred in 130 of 294 (44.2%) included RCTs. None of the articles mentioned the switching or provided justification.

429 registered primary outcomes were mapped to 1354 published outcomes, including 528 (39.0%) primary outcomes and 826 (61.0%) secondary outcomes. The main analysis supported the association between the nature of findings and the switching of primary outcomes ($F=10.0$, $P<0.01$) and the timing of registration as an effect modifier ($F=6.8$, $P<0.01$). When RCTs were prospectively registered, the odds of switching primary outcomes with negative findings were 2.34 (95%CI: 1.03 to 5.33) times the odds of switching primary outcomes with positive findings. When RCTs were retrospectively registered before trial completion, the odds of switching primary outcomes with negative findings were 9.69 (95%CI: 3.62 to 25.93) times the odds of switching primary outcomes with positive findings.

Conclusion and Relevance Registered primary outcomes with negative findings are more likely to be switched to secondary outcomes in the published journal articles. The timing of registration modifies this association as the strongest effect is observed among RCTs retrospectively registered before trial completion. Prospective registration should be promoted to detect and reduce primary outcome switching.

Introduction

Randomized controlled trials (RCTs), the pillar of evidence-based medicine, are a key tool to evaluate the efficacy and safety of health care interventions. An RCT usually incorporates multiple outcomes, of which the primary outcome is especially important to informing the overarching design, analysis, and interpretation.[1] Ideally, primary outcomes should be pre-specified and registered before the first participant is enrolled.[2,3] Any subsequent modification should be appropriately documented and reported to the research community.

Switching primary outcomes after recruitment has begun is prevalent.[4-6] Several factors, such as the sponsorship or financial ties related to the industry, may drive these changes.[7,8] Another factor which is widely suspected to influence primary outcome switching is the nature of findings as they develop; that is, whether the findings of primary outcomes are positive or statistically significant.[5] Switching primary outcomes based on the nature of findings may artificially amplify the probability of false positive findings, bias the interpretation of the overall result, and lead to adoption of new therapies with spurious benefits.[6,9,10]

Trial registries enable investigators to track the changes of primary outcomes over the course of a trial and scrutinize any discrepancies between trial protocols and subsequent publications.[11-13]Recently trial registries have been witnessing a proliferation of RCTs from China.[14,15] Trialists in China can register RCTs either in English registries, such as ClinicalTrials.gov (CT.gov), or

bilingual registries, such as the Chinese Clinical Trial Registry (ChiCTR). The versatility and dispersion of these RCTs provides a unique opportunity to evaluate the switching of primary outcomes and potential effect modifiers. The aim of this analysis is to evaluate the association between the nature of findings and the switching of primary outcomes, and whether this association varies by registry and the timing of registration.

Methods

In this retrospective cohort study, we retrieved RCTs sponsored by organizations located in mainland China from trial registries, identified the corresponding journal articles from bibliographic databases, compared the primary outcomes between trial registries and journal articles, and evaluated the factors associated with primary outcome switching. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[16] The study was not subject to institutional review board approval because all the data were open-source and no participant was involved.

Retrieve RCTs from Trial Registries

The method to retrieve registry records and journal articles of RCTs is described elsewhere.[17] Briefly, we retrieved RCTs from 17 primary registries recognized by the World Health Organization and the Drug Clinical Trial Registry Platform (DCTPR) sponsored by the China Food and Drug Administration (China FDA).[18,19] RCTs were retrieved if they evaluated drugs that were regulated by the United States Food and Drug Agency (US FDA) and/or the European Medicine Agency (EMA).[20,21] We only considered RCTs conducted between January 1, 2008 and December 31, 2014 to allow a minimum of 4.5 years from trial completion to publication.[22]

Identify Journal Articles from Bibliographic Databases

The corresponding journal articles from registered RCTs were searched through seven bibliographic databases, including PubMed, Embase, the Cochrane Central Register of Controlled Trials, the China National Knowledge Infrastructure (CNKI), SinoMed, the VIP information, and the Wanfang Data.[23] The search strategy, search terms, and the method to match registry records to journal articles are shown in Supplement Tables 1-3. We only included the main article of each RCT, defined as the article with the largest sample size, or the earliest article submitted to a journal if identical sample size was reported in multiple articles. The screening was conducted by two authors (YJ and DH) independently and adjudicated by a third author (JW) in case of discrepancy.

Map primary outcomes from Trial Registries to Journal Articles

We extracted all the outcomes labelled as 'primary' from trial registries and dissected them into five elements including domain (e.g., systolic blood pressure), specific measurement (e.g., a device at sitting position), specific metric (e.g., change from baseline), method of aggregation (e.g., mean or median), and time-points.[24] Registered primary outcomes were excluded if (1) the domain was not specified, such as *'efficacy'*, *'safety'*, etc.; (2) not related to the study intervention, e.g., baseline characteristics, etc.; and (3) duplicated with previous primary outcomes in the same trial. If RCTs were prospectively registered, i.e., registration occurred before recruitment started,[11] we only considered the latest version before recruitment started; if the RCTs were retrospectively registered, i.e., registration occurred after recruitment started, we only considered the earliest version.

Two authors (YJ and DH) independently searched the articles for published outcomes that were consistent with a registered primary outcome in terms of the elements. A registered primary outcome might fail to specify one or more elements and thus could be mapped to multiple published outcomes. For example, the registered primary outcome of *'the change of systolic blood pressure from baseline*', which lacked time-points, could be mapped to the published

outcomes measured at multiple time-points in the articles. We did not consider outcomes measured among subgroups.

Analysis plan

Exposure The exposure was the nature of findings of registered primary outcomes (positive vs. negative). We defined positive findings as favoring the study hypothesis with statistical significance. For example, a superiority trial was positive when the experimental drug was significantly superior over the comparator. We defined negative findings as not statistically significant or contradictory to the study hypothesis.

Outcome The outcome of this study was defined as a registered primary outcome of an RCT being switched to a secondary outcome in the published journal article. In the main analysis, we considered an outcome in an article as 'primary' if it was designated as such or used in the power calculation in case of no designation.

Effect Modifiers We classified the timing of registration into three categories: (1) prospective; (2) retrospective before trial completion, i.e., the trial was registered after recruitment started but before it was completed; and (3) retrospective after trial completion, i.e., the trial was registered after it was completed. We assumed the association between the nature of findings and primary outcome switching would be the strongest when RCTs were prospectively registered, while the weakest when RCTs were retrospectively registered after trial completion, because we expected those registered retrospectively could have already switched primary outcomes before registration. We also hypothesized that the association between the nature of findings and primary outcome switching might vary across registries.

Confounders Three possible confounders were pre-specified, including funding source (industry vs. non-industry), sample size (>=100 or <100), and number of recruiting centers per trial (multiple vs. single).[7,8,25,26]

Measurements of Associations We hypothesized that registered primary outcomes with negative findings were more likely to be downgraded to secondary outcomes in the articles than those with positive findings. Odds ratio (OR) were estimated by multi-level logistic models with random intercept to account for two levels of correlation: multiple registered primary outcomes within the same trial and multiple published outcomes mapped from the same registered primary outcome. Considering outcome reporting bias, i.e., negative outcomes are less likely to be published than positive outcomes, the assumption of data missing at random would not hold in case a registered primary outcome was missing from the article. Thus, the main analysis was conducted on complete cases, while two sensitivity analyses were conducted on the best-case and worst-case scenarios regarding the missingness, respectively.

We conducted two comparisons across registries: (1) the average number of registered primary outcomes per trial; (2) the proportion of registered primary outcomes with specified time-points.[3] We also compared the outcomes reported as 'primary' with the ones used in power calculations in the articles.

In the first sensitivity analysis, we only considered outcomes designated as primary in the articles, while excluding the ones identified from power calculations because we expected differences between those two methods of identifying primary outcomes. In the second sensitivity analysis, the registered primary outcomes missing from the articles were explored under a worst-case scenario: If a registered primary outcome was published as primary in the article with unclear findings, we assumed it to be negative; If a registered primary outcome was reported as secondary in the article with unclear findings, we assumed it to be positive; If a registered primary outcome was completely missing from the article, we assumed it to be published as secondary and positive. The third sensitivity analysis explored the best-case scenario against all the assumptions in the second sensitivity analysis.

The between-group comparisons were conducted by Mann-Whitney test. Statistical significance was defined as a P value less than 0.05 for the main effect and 0.1 for interaction. SAS® 9.4 was used for data cleaning and analysis.

Results

Characteristics of Included RCTs

The search of trial registries and bibliographic databases was conducted from March to August 2019 (Figure 1). In total 891 RCTs evaluating drug(s) were retrieved from registries, of which 470 (52.7%) were matched to at least one journal article. We subsequently excluded 203 RCTs owing to missing registration date (n=16), unclear primary outcome in the registry (n=5), or unclear primary outcome in the article (n=155). 294 RCTs were included in the analysis, including 187 from ChiCTR, 103 from CT.gov, and 4 from ISRCTN. RCTs from CT.gov and ISNCTR were combined to form a new category referred to as English registries.

The characteristics of included RCTs are shown in Table 1. More than a third of RCTs were prospectively registered (113/294, 38.44%), followed by retrospective registration before trial completion (108, 36.73%) and retrospective registration after trial completion (73, 24.83%). Most RCTs were funded by non-industrial organizations (237, 80.61%), recruited more than 100 participants (194, 65.99%), and were conducted in a single institution (198, 67.35%). Meanwhile, RCTs from ChiCTR registered more primary outcomes than English registries (2.40 vs. 1.20, χ^2=38.52, P<0.01). 47 (25.13%) RCTs from ChiCTR registered at least 3 primary outcomes, higher than English registries (OR=6.85, 95%CI: 2.63-17.83), where only 5 (4.67%) registered at least 3 primary outcomes.

Elements of Registered Primary Outcomes

A total of 577 primary outcomes were retrieved from the registries, including 449 (77.82%) from ChiCTR and 128 (22.18%) from English registries. Only 3.56% primary outcomes from ChiCTR included the time-points, much lower than English registries (96.09%).

Discrepancy between Primary Outcome Designation and Power Calculation

In 182 articles the authors simultaneously designated primary outcomes and reported power calculations regarding 496 outcomes in total. 246 (49.60%) primary outcomes were both designated and used in power calculations, 236 (47.58%) were designated but missing from power calculations, while 14 (2.82%) were used in power calculations but not designated as primary outcomes.

Discrepancies between Trial Registries and Journal Articles

We detected primary outcome switching in 130 of 294 (44.20%) RCTs, including 103 (55.08%) from ChiCTR and 27 (25.23%) from English registries. None of the articles provided a rationale for the switching. Among the 577 registered primary outcomes, 429 (74.35%) were mapped to 1354 published outcomes in the articles, including 528 (39.00%) primary outcomes and 826 (61.00%) secondary outcomes. The remaining 148 (25.65%) registered primary outcomes were considered missing.

The main analysis supported the association between the nature of findings and primary outcome switching ($F=9.99$, $P<0.01$), along with the timing of registration being an effect modifier ($F=6.76$, $P<0.01$). However, we did not find evidence supporting that the association between the nature of findings and primary outcome switching varied in registries ($F=0.21$, $P=0.65$). When the RCTs were prospectively registered, the odds of switching primary outcomes with negative findings were 2.34 (95%CI: 1.03 – 5.33) times the odds of switching primary outcomes with positive findings. When the RCTs were retrospectively registered before trial completion, the odds of switching primary outcomes with negative findings were 9.69

(95%CI: 3.62 – 25.93) times the odds of switching primary outcomes with positive findings. The ORs were consistent across registries while the magnitude was slightly higher among RCTs from ChiCTR (Table 2).

There was evidence supporting the registry and the number of recruiting centers as two confounders, i.e., the odds of switching primary outcomes from ChiCTR was 5.11 (95%CI: 2.32 – 11.26) times the odds of switching primary outcomes from English registries; the odds of switching primary outcomes from RCTs conducted in one recruiting center was 2.79 (95%CI: 1.11-7.02) times the odds of switching primary outcomes from RCTs conducted in multiple recruiting centers.

The first sensitivity analysis produced similar results to the main analysis, although the magnitude of associations decreased slightly (Supplemental Table 4). The second sensitivity analysis under the worst-case scenario still supported the association between the nature of findings and primary outcome switching among RCTs which were retrospectively registered before trial completion (Supplemental Table 5). The third sensitivity analysis reaffirmed the findings from the main analysis with strengthened associations (Supplemental Table 6).

Discussion

Our study supported the hypothesis that trialists were more likely to downgrade a registered primary outcome to a secondary outcome in publications if the findings were negative.

We found that 26% of RCTs from English registries (mainly CT.gov) switched primary outcomes – a percentage slightly lower than a previous study, in which 31.7% of clinical trials from CT.gov switched primary outcomes after registration.[4] We observed a much higher probability of primary outcome switching among RCTs from ChiCTR (55%), mainly because in ChiCTR, RCTs tended to register multiple primary outcomes. The overall percentage of switching (44%)

was comparable to cohorts of trials submitted to ethics committees.[27-30] However, we only measured one type of switching. It is likely that the overall frequency of primary outcome switching would be higher than RCTs outside of China if we had considered all possible types of switching, e.g., a registered secondary outcome was upgraded to a primary outcome in the publication or a new outcome never appearing in the registry was added as a primary outcome in a publication.[27]

We also hypothesized that the stage of recruitment at the time of registration (i.e., prospective or retrospective registration) would be related to the likelihood of switching primary outcomes. We assumed that before the first patient was enrolled, the findings were challenging to predict, therefore a subsequent switching was possible when the findings of the registered primary outcome were negative. On the other hand, as recruitment began and continued, data from participants gradually accumulated to facilitate trialists to predict the findings. At this stage, trialists would be able to register an outcome, which was likely to bear positive findings, as primary in the registry, thereby reducing the risk of switching it thereafter. However, our analysis contradicted this assumption, instead suggesting the strongest association was among trials registered retrospectively rather than at the beginning of a trial. A possible explanation is that trialists who registered their trials beforehand might be more aware of the guidelines and regulations to conduct high-quality trials and thus were more willing to abide by the rules and retain the pre-defined primary outcomes regardless of the findings.

We also hypothesized that the association between the nature of findings and the likelihood of switching primary outcome varied across registries because ChiCTR was different from English registries in many aspects; for example, our study showed the data quality was much better in English registries than ChiCTR in terms of specifying time-points. Despite the differences, we found little evidence supporting the heterogeneity in the association across registries. This suggests that improving data quality of registries may not reduce the association between the

nature of findings and primary outcome switching. However, we did find evidence supporting that primary outcome switching occurred more often among RCTs from ChiCTR, which may be attributable to the tendency of defining multiple primary outcomes.

Our study reiterated the importance of registering clinical trials prospectively to enable the medical community to track and audit any changes over time.[11,13,31] Currently less than 15% of RCTs were registered,[32] of which more than half were retrospective registration,[17] posing a serious challenge to researchers and policy makers. Although China FDA – the only government agency supervising clinical trials in China – has required registration of clinical trials submitted in support of marketing license of medical products since 2013,[19] such trials constitute only a small fraction of all trials in China, where publications have been dominated by post-marketing trials. Promoting and expanding registration would be the most effective approach to addressing the problem, either by legislation from government agencies or broad requirement by research institutes and academic journals. Unfortunately, registration can only facilitate detecting, rather than reducing, the switching of primary outcomes.[11] Other smaller step may be more actionable and have an impact: none of the articles in our study mentioned or justified their switching of primary outcomes, implying that this had been overlooked by reviewers and journal editors. We recommend reviewers to routinely compare registry with manuscript of RCTs. Authors should be required by either reviewers or journal editors to explain any discrepancies identified.

Our study has several limitations. First, a larger sample would enable more precise estimation of the associations. Second, a quarter of the registered primary outcomes were missing from the linked publications. Although we demonstrated the robustness of the main analysis by assuming a worst-case scenario, the complete-case analysis would likely underestimate the associations due to outcome reporting bias,[27] the 'real' association including the missing primary outcomes should be somewhere between the main analysis and sensitivity analysis under the

best-case scenario. Third, although we developed a systematic method to search the literature and match journal articles, it is possible that we mismatched or overlooked some articles. Fourth, we allowed RCTs at least 4.5 years from trial completion to publication, which might not be adequate in some cases. Considering the large effect size, we believe capturing a few more trials would be unlikely to affect our conclusions. Finally, we restricted our study sample to RCTs that evaluated drugs only within mainland China. It is unclear whether our conclusions can be extrapolated to other interventions, such as traditional Chinese medicine, or RCTs outsides of China.[33] Future research is needed to explore the association in other settings, more factors playing a role in the association, and whether the association changes overtime.

Conclusion

Our study supports the hypothesis that the nature of findings plays a role in the likelihood of changing primary outcome among RCTs. Additionally, the timing of registration modifies this association as we observed the strongest effect among RCTs retrospectively registered before trial completion.

Table 1 Characteristics of Included RCTs

Characteristics	Category	ChiCTR		English Registries		Total	
		No.	%	No.	%	No.	%
Number		187	100	107	100	294	100
Timing of Registration	Prospective	73	39.04	40	37.38	113	38.44
	Retrospective Before Trial Completion	60	32.09	48	44.86	108	36.73
	Retrospective After Trial Completion	54	28.88	19	17.76	73	24.83
Funding	Industry	37	19.79	20	18.69	57	19.39
	Non-Industry	150	80.21	87	81.31	237	80.61
Sample Size	<100	66	35.29	34	31.78	100	34.01
	>=100	121	64.71	73	68.22	194	65.99
Number of Centers	Multiple	50	26.74	46	42.99	96	32.65
	Single	137	73.26	61	57.01	198	67.35
No. of Registered Primary Outcomes	Single Primary Outcome	98	52.41	94	87.85	192	65.31
	2 Co-Primary Outcomes	42	22.46	8	7.48	50	17.01
	>=3 Co-Primary Outcomes	47	25.13	5	4.67	52	17.69

Abbreviations

RCT: Randomized Controlled Trials; ChiCTR: Chinese Clinical Trial Registry; OR: Odds Ratio

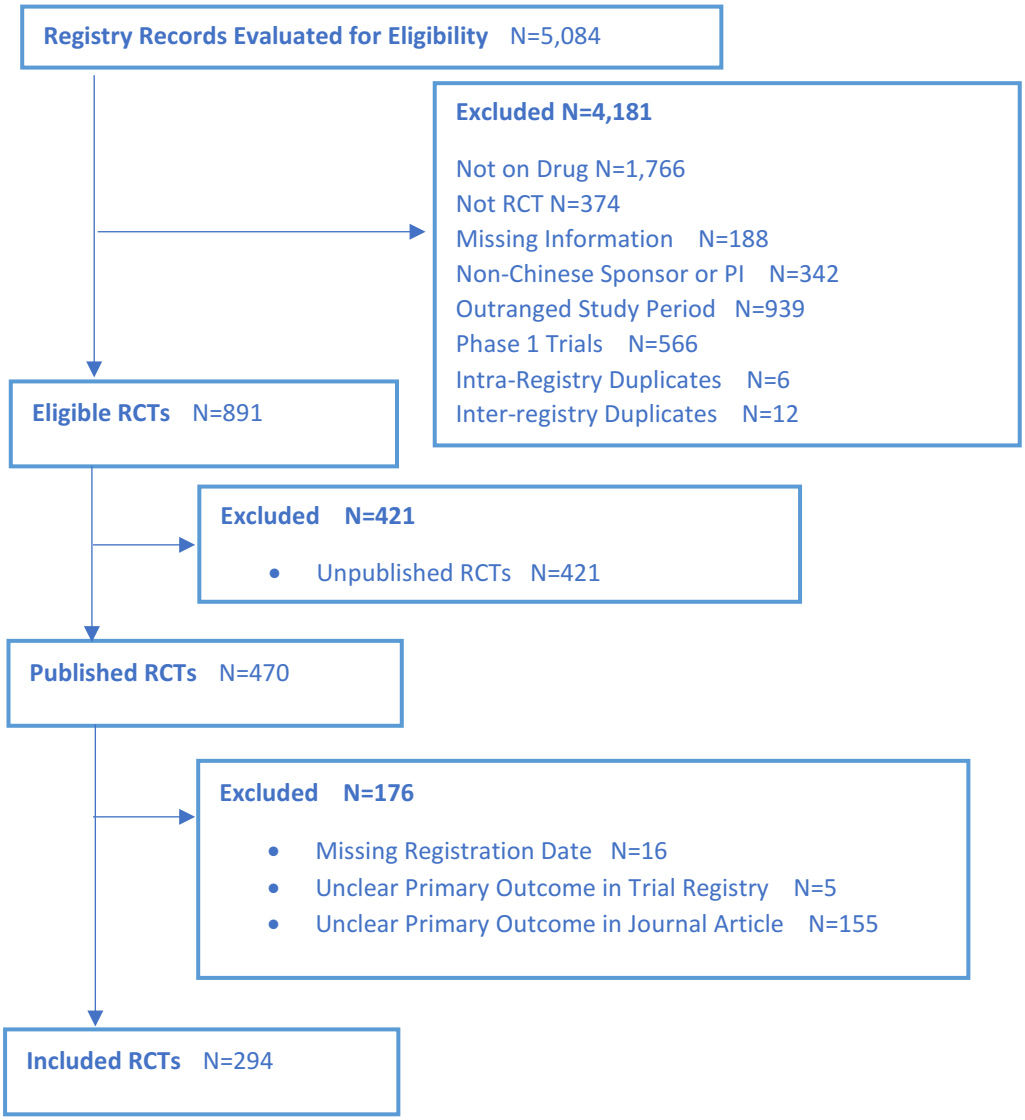
Table 2 Factors Associated with Discrepancy between Registered and Published Primary Outcomes: Primary Analysis

Factor	Level	Stratum	OR	95%CI	P Value
Nature of the Findings	Negative vs. Positive	Prospective Registration	2.34	1.03 – 5.33	0.04
		Retrospective Before Trial Completion	9.69	3.62 – 25.93	<0.01
		Retrospective After Trial Completion	0.80	0.30 – 2.13	0.66
		ChiCTR & Prospective Registration	2.69	1.27 – 5.73	0.01
		ChiCTR & Retrospective Before Trial Completion	11.16	3.95 – 31.49	<0.01
		ChiCTR & Retrospective After Trial Completion	0.93	0.37 – 2.29	0.87
		English Registries & Prospective Registration	2.03	0.59 – 6.95	0.26
		English Registries & Retrospective Before Trial Completion	8.41	2.38 – 29.67	<0.01
		English Registries & Retrospective After Trial Completion	0.70	0.18 – 2.68	0.6
Registry	ChiCTR vs. English Registries		5.11	2.32 – 11.26	<0.01
Timing of Registration	Prospective vs. Retrospective After Trial Completion		0.52	0.22 – 1.20	0.13
	Retrospective Before Trial Completion vs. Retrospective After Trial Completion		0.51	0.23 – 1.15	0.11
Sample Size	>=100 vs. <100		0.52	0.25 – 1.08	0.08
Funding	Non-Industry vs. Industry		1.12	0.41 – 3.03	0.83
Number of Recruiting Centers	Single vs. Multiple		2.79	1.11 – 7.02	0.03

Abbreviations

ChiCTR: Chinese Clinical Trial Registry; OR: Odds Ratio

Figure 1 Identifying Eligible RCTs



Chapter 2

Assessment of Language Bias and Indexing Bias Among Chinese-Sponsored Randomized Controlled Trials

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Abstract

Importance Language bias and indexing bias may exist among Chinese-Sponsored Randomized Controlled Trials (CS-RCTs). Such bias may threaten the validity of systematic reviews.

Objective To evaluate the existence of language bias and indexing bias among CS-RCTs on drug interventions.

Design In this retrospective cohort study we retrieved eligible CS-RCTs from trial registries and searched bibliographic databases to determine their publication status. The search and analysis were conducted from March to August 2019.

Setting Primary trial registries recognized by the World Health Organization (WHO) and the Drug Clinical Trial Registry Platform (DCTRP) sponsored by the China Food and Drug Administration (China FDA).

Participants Eligible CS-RCTs were on drug interventions and conducted between January 2008 and December 2014.

Exposure Individual CS-RCTs with positive (versus negative) results.

Main Outcomes and Measures For assessing language bias, the main outcome was the language of the journal where CS-RCTs were published (English versus Chinese). For indexing bias, the main outcome was the language of bibliographic database where the CS-RCTs were indexed (English versus Chinese).

Results We identified 891 eligible CS-RCTs. Four hundred and seventy CS-RCTs were published by August 2019, of which 368 (78.3%) were published in English. Among CS-RCTs registered in the Chinese Clinical Trial Registry (ChiCTR), positive CS-RCTs were 3.92 (95%CI: 2.20-7.00) times more likely to be published in English than negative CS-RCTs; among CS-RCTs registered in English registries, positive CS-RCTs were 3.22 (95%CI: 1.34-7.78) times more likely to be published in English than negative CS-RCTs. These findings suggest the existence of language bias. Among CS-RCTs registered in ChiCTR, positive CS-RCTs were 2.89 (95%CI: 1.55-5.40) times more likely to be indexed in EBDs than negative CS-RCTs; among CS-RCTs registered in English registries, positive CS-RCTs were 2.19 (95%CI: 0.82-5.82) times more likely to be indexed in EBDs than negative CS-RCTs. These findings support the existence of indexing bias.

Conclusions and Relevance Our study indicates the existence of language bias and indexing bias among registered CS-RCTs on drug interventions. This may distort evidence-synthesis towards more positive results of drug interventions.

Introduction

In non-English-speaking countries, researchers can choose to publish randomized controlled trials (RCTs) in either English journals or journals in their native language. It is established that RCTs with positive results ("positive RCTs") are more likely to be published in English journals: a phenomenon termed language bias [1]. This tendency may lead to disproportionally more positive RCTs in the English literature and consequently more negative RCTs in the non-English literature [2].

Ideally this bias would not threaten the validity of systematic reviews as reviewers should comprehensively search for all the existing evidence, regardless of the language [1]; however, estimates indicate that almost 40% of systematic reviews are reportedly restricted to English language articles indexed in English bibliographic databases (EBDs) [3]. This raises the concern that such reviews may miss negative RCTs which are only published in the non-English literature, leading to biased evidence [4].

Recently scientific publications from Mainland China have been surging [5]. Publications of RCTs sponsored by researchers in Mainland China, referred to as CS-RCTs, are also split between English and Chinese journals ("English CS-RCTs" and "Chinese CS-RCTs") [6]. However, limited evidence is available regarding language bias among CS-RCTs. It's unknown whether we should include Chinese CS-RCTs indexed in EBDs to reduce the effect of speculated language bias.

A further challenge, and one which is more difficult to address, is that most Chinese journals have not been indexed in EBDs due to large quantity and varying quality [7]. This implies that systematic reviewers have to not only remove language restrictions from searching EBDs but also actively search Chinese bibliographic databases (CBDs) to capture all Chinese CS-RCTs, a practice seldomly adapted by the systematic review community [8]. Bias may exist if Chinese CS-RCTs with positive results are more likely to be indexed in EBDs than their negative counterparts which are more commonly seen in CBDs. We refer this potential residual of language bias to indexing bias.

Currently the Cochrane Handbook for Systematic Reviews of Interventions only recommends searching CBDs for systematic reviews of Chinese herbal medicine [1]. It's unknow whether the recommendation should be extended to drug interventions. The objective of this study was to evaluate the existence of language bias and indexing bias among CS-RCTs on drug interventions to inform the potential update of the recommendation.

Methods

In this retrospective cohort study, we retrieved CS-RCTs from trial registries and searched bibliographic databases to determine their publication status. Two hypotheses were pre-defined: (1) positive CS-RCTs were more likely to be published in English than negative CS-RCTs (language bias), and (2) positive CS-RCTs were more likely to be indexed in EBDs (indexing bias). We followed the STROBE reporting guidelines [9].

Identifying CS-RCTs from Trial Registries

We retrieved CS-RCTs from all 17 primary registries recognized by the World Health Organization [10] and the Drug Clinical Trial Registry Platform (DCTPR) sponsored by the China Food and Drug Administration (China FDA) [11].

A substance was considered a drug if recognized and regulated by the United States Food and Drug Agency (US FDA) and/or the European Medicine Agency (EMA) [12,13]. We included all CS-RCTs that started after January 1, 2008 and completed before December 31, 2014 to allow a minimum of 4.5 years from trial completion to publication [14].

We excluded Phase 1 trials (including bioequivalence and pharmacokinetics studies) and CS-RCTs missing the study period or RCTs with an unclear study interval (e.g., end date before the start date), any unnamed experimental drug, principal investigator (PI), or sponsor in the registries.

Identify Journal Articles from Bibliographic Databases

We only included journal articles produced from eligible CS-RCTs. Conference abstracts, research letters, and dissertations were not included. Publications of protocols, subgroup analyses, secondary analyses, and meta-analyses were also excluded.

Based on previous studies [14,15], we developed search strategies for individual CS-RCTs with informationists from the Welch Medical Library at the Johns Hopkins University and from the Institute of Information/Medical Library at the Peking Union Medical College (Supplement 1) [16,17]. We expanded the search terms with synonyms and spelling variations to increase sensitivity. The search terms were tailored and organized for each bibliographic database based on the database's specific syntax (Supplement 2). Seven bibliographic databases were subsequentially searched: three English ones (PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL)); and four Chinese ones: the China National Knowledge Infrastructure (CNKI), SinoMed, the VIP information, and the Wanfang Data) [18].

We conducted a 4-step process to identify matches of eligible CS-RCTs. First, we searched bibliographic databases to retrieve citations; second, we screened the citations for eligible CS-RCTs; third, we downloaded PDFs of possibly eligible trials; and fourth, we matched the PDFs

with the registry records of eligible CS-RCTs. The criteria for screening and matching are shown in Supplement 3.

The journal articles were classified as confirmed matches and probable matches according to the similarity between journal articles and registry records. Confirmed matches indicated the journal articles were consistent with the registry records, while probable matches indicated the journal articles were similar to the registry records but differed on or lacked only one data item. The primary analysis was conducted among the confirmed and probable matches, while a sensitivity analysis was conducted among the confirmed matches only.

Two authors independently searched bibliographic databases and identified matching PDFs of eligible CS-RCTs. Discrepancies were discussed and resolved by a third author. If multiple journal articles existed, we only considered the one with the largest sample size, or the earliest one if identical sample size was reported in multiple articles.

Analysis plan

Exposure The exposure was the positivity of individual CS-RCTs (positive versus negative) according to the CS-RCT's primary outcome reported in the journal article(s) [19]. If multiple primary outcomes were reported in a CS-RCT, we selected the first one reported in the result section. If no primary outcome was defined, the selection of the CS-RCT's primary outcome was based on the following hierarchical order: the first outcome used in the sample size calculation, the first outcome defined in the study objective, or the first outcome reported in the results section. When the time point was not specified for the CS-RCT's primary outcome which was measured at multiple time points, we considered the last time point in our main analysis and the first time point in sensitivity analyses.

We defined a positive result as favoring the experiment group with statistical significance in superiority trials or showing no difference between treatment groups for equivalence or non-

inferiority trials. Results which were not statistically significant, significantly favored the control group, or failed to show equivalence/non-inferiority were defined as negative.

Outcome Two main outcomes were defined: the language of the publication (English versus Chinese) and the language of the bibliographic database where the publication was indexed (English versus Chinese). An article published in both Chinese and English was considered published in English; similarly, an article indexed in both EBDs and CBDs was considered indexed in EBDs. We assumed all English articles were indexed in EBDs, but Chinese articles were possibly indexed in EBDs or CBDs.

Measurements of Associations Bias was estimated by relative risk (RR), including point estimates and 95% confidence intervals (CIs). A RR larger than one indicated that positive CS-RCTs were more likely to be published in English or indexed in EBDs than negative CS-RCTs. RRs were estimated using log binomial models with five covariates: sample size (<100 versus ≥100), funding source (industry versus non-industry), study design (superiority versus non-inferiority/equivalence), number of recruitment centers (single versus multiple), and registration type (prospective versus retrospective) [20-21]. Industrial funding was considered as long as one funder was from industry; prospective registration was considered when registration occurred before the first participant was recruited [22]. We included an interaction term in the models to evaluate the heterogeneity of bias across registries. Statistical significance was defined as a P value smaller than 0.05 for the main effect and 0.1 for interaction. SAS® 9.4 was used for data cleaning and analysis.

Results

The search through trial registries and bibliographic databases was conducted from March to August 2019. Among the 17 primary registries and DCTRP, five were found to include eligible

CS-RCTs: the Chinese Clinical Trial Registry (ChiCTR), ClinicalTrials.gov, ISRCTN, the Australia New Zealand Clinical Trials Registry (ANZCTR), and DCTRP. In total 5,084 CS-RCTs were retrieved from these trial registries and screened for eligibility. Eventually 891 eligible CS-RCTs were identified, 470 (52.7%) of which had been published in 229 English journals and 72 Chinese journals. The screening results are shown in Figure 1.

Characteristics of CS-RCTs

Among the 470 journal articles corresponding to 470 CS-RCTs, 368 (78.3%) were published in English, while 102 (21.7%) were in Chinese; 432 (91.9%) were confirmed matches to registry records, while 38 (8.1%) were probable matches. Thirty of 38 (78.9%) probable matches were published in Chinese. The matching results are shown in Supplement 3.

The distribution of CS-RCTs across bibliographic databases is shown in Table 1. The three EBDs only indexed a small proportion of Chinese articles, ranging from 21.6% by PubMed to 23.5% by Embase and CENTRAL. The low coverage of CNKI was mainly due to unindexed or partially unindexed medical journals sponsored by the Chinese Medical Association.

Most (306, 65.1%) CS-RCTs were registered in ChiCTR, followed by ClinicalTrials.gov (143, 30.4%), DCTRP (13, 2.8%), ISRCTN (4, 0.9%), and ANZCTR (1, 0.2%). The CS-RCTs in DCTRP, ISRCTN, and ANZCTR were too few to be analyzed separately. We expected that the two biases would be similar across ClinicalTrials.gov, ISRCTN, and ANZCTR, so we combined CS-RCTs from these three registries to form a new category: 'English registries'. On the other hand, DCTRP, which was only available in Chinese and was not a primary registry, was excluded from the inferential analyses.

Of the 470 CS-RCTs, 323 (69.0%) were positive, 2 (0.4%) were excluded from inferential analyses due to unknown positivity (no inter-group comparison), 286 (60.9%) recruited at least 100 participants, 322 (68.5%) were conducted at a single center, 377 (80.2%) were supported

by non-industry funding, 315 (67.0%) were retrospectively registered, and 442 (94.4%) were superiority trials.

The distribution of covariates, including the sample size, funding source, study design, number of recruitment centers, and registration type, was similar between English and Chinese CS-RCTs (Supplement 4); the distribution of covariates among CS-RCTs indexed in EBDs was similar to the ones only indexed in CBDs, although the number of positive CS-RCTs indexed in CBDs was slightly larger than the negative CS-RCTs (Supplement 5).

Language Bias

Four hundred and sixty-eight CS-RCTs were included for this analysis. As shown in Table 2, positive CS-RCTs were more likely to be published in English and were more likely to be indexed in EBDs than CS-RCTs published in Chinese. After adjusting for covariates, positive CS-RCTs were more commonly published in English than negative CS-RCTs. The RRs were 3.92 (95%CI: 2.20-7.00) and 3.22 (95%CI: 1.34-7.78) among CS-RCTs registered in ChiCTR or English registries, respectively (Table 3). The interaction between registry and positivity of CS-RCTs was not statistically significant (P=0.13), indicating no evidence of heterogeneity of language bias across registries. Other factors associated with increased likelihood of being published in English among CS-RCTs were sample size of >= 100 (RR 2.09; 95%CI: 1.19-3.67), single center as opposed to multicenter trial (RR 1.85; 95%CI: 1.01-3.41), and financial support from a non-industry source as compared to an industrial source (RR: 1.99; 95%CI: 1.06-3.75).

Indexing Bias

Four hundred and sixty-eight CS-RCTs were included for this analysis. As shown in Table 2, English CS-RCTs or CS-RCTs indexed in EBDs were more likely to be positive than Chinese CS-RCTs or CS-RCTs only indexed in CBDs. After adjusting for covariates, positive CS-RCTs were more commonly indexed in EBDs than negative CS-RCTs. The RRs were 2.89 (95%CI:

1.55-5.40) and 2.19 (95%CI: 0.82-5.82) among CS-RCTs registered in ChiCTR or English registries, respectively (Table 3). The interaction between registry and language of bibliographic databases was not statistically significant (P=0.22), indicating no evidence of heterogeneity of indexing bias across registries. The only other factor associated with an increased likelihood of being indexed in EBDs among CS-RCTs was sample size of $\geq$ 100 (RR: 2.04; 95%CI: 1.11-3.72).

Sensitivity Analysis

Two sensitivity analyses were conducted. When only confirmed matches (n = 432) were analyzed, the RRs increased regarding language bias (4.14 (95%CI: 2.09-8.21) among ChiCTR and 3.58 (95%CI: 1.32-9.72) among English registries) and decreased regarding indexing bias (2.47 (95%CI: 1.15-5.34) among ChiCTR and 1.92 (0.62-6.04) among English registries). When the first assessment of the CS-RCTs' primary outcomes was analyzed (rather than the last assessment at the end of follow-up), the RRs increased regarding both language bias (5.34 (95%CI: 3.00-9.68) among ChiCTR and 3.73 (95%CI: 1.53-9.07) among English registries) and indexing bias (95%CI: 4.76 (2.49-9.08) among ChiCTR and 2.67 (95%CI: 1.01-7.11) among English registries).

Discussion

Our study supports the existence of language bias and indexing bias among CS-RCTs registered in trial registries. As hypothesized, positive CS-RCTs were more likely to be published in English or indexed in EBDs as compared with negative CS-RCTs.

Language Bias

Reputation, job prospects, as well as academic progress may critically depend on publishing in English journals among Chinese researchers [23,24]. Positive CS-RCTs are more likely to be submitted to English journals as they typically have a higher chance of being accepted; accordingly, English journals contain more positive CS-RCTs than their Chinese counterparts.

Theoretically, language bias disappears if all clinical trials shift to be published in English. This ideal has been echoed by a trend towards publishing in English in some countries, such as Germany [25]. With the average number of RCTs per German journal decreasing from a maximum of 11.2 annually between 1970 and 1986 to only 1.7 annually between 2002 and 2004, language bias from German-speaking countries may no longer be a concern.

We did not detect such a trend among CS-RCTs. According to an ongoing study, the number of CS-RCTs published in Chinese may be as many as 44,000 in 2016, as opposed to fewer than 1,000 being published in English [26]. The deep gap between the Chinese and English literature has allowed significant space for language bias to develop.

Several studies attempted to evaluate the effect of language bias based on non-English trials included in systematic reviews [27-28]. Since most systematic reviews were constrained to working within EBDs only, what those studies measured was a fraction of language bias – the difference between English and non-English trials indexed in EBDs. The effect of language bias cannot be comprehensively evaluated unless non-English trials, especially the ones not indexed in EBDs, are included and evaluated.

Indexing Bias

As the primary source for systematic reviewers, EBDs may index some non-English literature but indeed they vary in the amount and scope. The Cochrane Handbook for Systematic reviews and the United States Institute of Medicine Guidelines for Systematic Reviews have recommended including non-English literature indexed in EBDs [1,29]. Including non-English trials

indexed in EBDs may not eliminate the effect of language bias but could reduce it to the scope of indexing bias.

To date EBDs do not represent the Chinese literature. This is problematic because an ongoing study shows more than 10,000 clinical trials have been published out of China in 2016 [26]. However, Embase only indexes 80 Chinese journals [7].

While we did not simulate actual systematic reviews it appears plausible that, due to language and indexing bias, drug interventions might appear more positive than they are when existing evidence is synthesized, for example in systematic reviews.

How to Eliminate the Effect of Language Bias Regarding CS-RCTs

The effect of language bias regarding CS-RCTs might be eliminated if reviews comprehensively searched CBDs, or if major EBDs would index all Chinese literature, or if all CS-RCTs would be appropriately registered with results. There are, however, layers of complexity that warrant appreciation. There has been a discussion over whether scientists should search CBDs when conducting systematic reviews [8,30]. Our study tipped the scales in this proposition's direction: including Chinese literature may reduce bias and shrink confidence intervals of the estimates. Currently the Cochrane Handbook for Systematic Reviews of Interventions only recommends searching CBD for topics related to complementary medicine or Chinese medicine [1], but our results suggest that it might be prudent to expand recommendations to studies on drug interventions as well.

The reporting quality of Chinese CS-RCTs was low [6,31,32], which some may argue is a reason to not use Chinese CS-RCTs in systematic reviews. However, reporting quality may not completely represent the actual scientific quality [33]. One study found no difference between one systematic review mainly using English-language trials and another one mainly using Chinese-language trials on the same topic [8]. It is the researchers' decision to include or not include those

trials (i.e., trials published in Chinese and/or indexed in CBDs) based on reporting quality, but it might be too simplistic to just ignore them.

Limitations

There are several limitations to our study. First, we searched seven prominent but not all bibliographic databases [34]. Second, our search strategy relied on the information in trial registries, which may be inaccurate and/or incomplete [35,36]. Third, less than 15% of Chinese articles reported registration [6,42,46], indicating CS-RCTs in trial registries may not be representative of all CS-RCTs in the time period addressed. At this moment it is unclear how much this study can be generalized to all CS-RCTs. Last, we studied language bias and indexing bias from the level of the entire RCT community, but we did not assess whether such biases might have effects on the conclusion of individual systematic reviews. Such simulation or empirical studies might further elucidate the extent and direction of systematic error introduced by language and indexing bias.

Conclusion

Our study indicates the existence of language bias and indexing bias among CS-RCTs in trial registries. This might threaten the validity of evidence synthesis. When synthesizing evidence, drug interventions might appear more favorable than in reality due to language and indexing bias. Removing language restrictions and actively searching CBDs may reduce the effect of these two biases.

Table 1 Coverage of Journal Articles by Bibliographic Databases

Bibliographic Database	English Article (Total=368)				Chinese Article (Total=102)				All Article (Total=470)			
	Indexed		Unindexed		Indexed		Unindexed		Indexed		Unindexed	
	No.	%	No.	%	No	%	No.	%	No.	%	No.	%
EBD												
PubMed	357	97.0	11	3.0	22	21.6	80	78.4	379	80.6	91	19.4
Embase	364	98.9	4	1.1	24	23.5	78	76.5	388	82.6	82	17.4
CENTRAL	348	94.6	20	5.4	24	23.5	78	76.5	372	79.2	98	20.1
CBD												
SinoMed	-		-		102	100.0	0	0.0	-		-	
CNKI	-		-		66	64.7	36	35.3	-		-	
VIP Data	-		-		100	98.0	2	2.0	-		-	
Wanfang Data	-		-		101	99.0	1	1.0	-		-	

EBD: English Bibliographic Database; CENTRAL: Cochrane Controlled Register of Trials; CBD: Chinese Bibliographic Database; CNKI: China National Knowledge Infrastructure.

Table 2 Positivity of CS-RCTs by Trial Registry and Bibliographic Database

Trial Registry	English Article		Chinese Article		EBD		CBD	
	No.	%	No.	%	No.	%	No.	%
ChiCTR								
Positive	180	85.3	31	14.7	186	88.2	25	11.8
Negative	56	59.6	38	40.4	67	71.3	27	28.7
Total	236	77.4	69	22.6	253	83.0	52	17.0
English Registries								
Positive	91	87.5	13	12.5	93	89.4	11	10.6
Negative	32	69.6	14	30.4	37	80.4	9	19.6
Total	123	82.0	27	18.0	130	86.7	20	13.3
DCTRP								
Positive	5	62.5	3	37.5	6	75.0	2	25.0
Negative	2	40.0	3	60.0	4	80.0	1	20.0
Total	7	53.9	6	46.1	10	76.9	3	23.1
Total								
Positive	276	85.5	47	14.5	285	88.2	38	11.8
Negative	90	62.1	55	37.9	108	74.5	37	25.5
Total	366	78.2	102	21.8	393	84.0	75	16.0

CS-RCTs: Chinese-Sponsored Randomized Controlled Trials; ChiCTR: Chinese Clinical Trial Registry; DCTRP: Drug Clinical Trial Registry Platform.

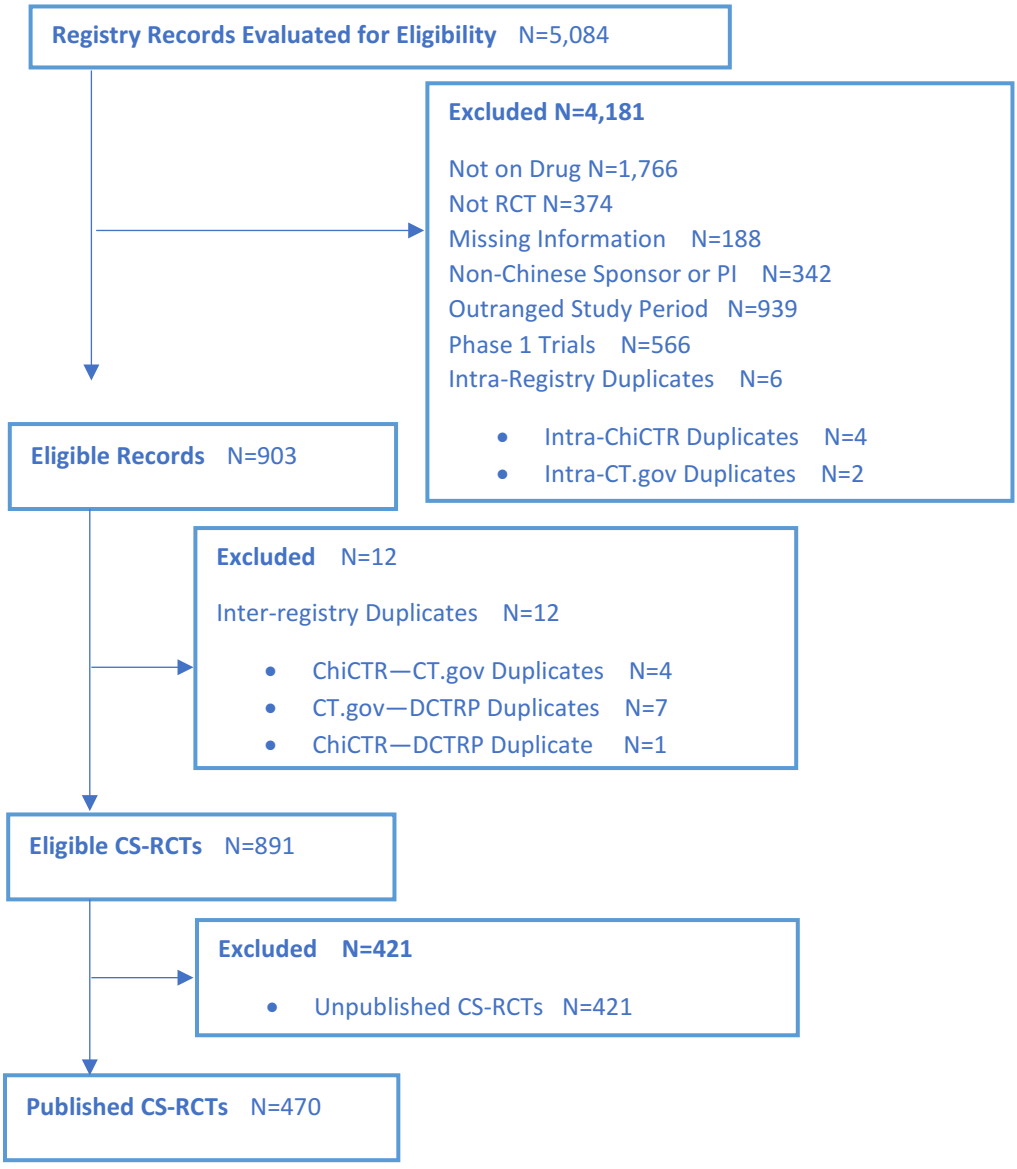
Table 3 Factors Associated with Language Bias and Indexing Bias

Factor	Language Bias			Indexing Bias		
	RR	95% CI	P Value	RR	95% CI	P Value
Positivity						
ChiCTR						
Positive	3.92	2.20-7.00	<0.001	2.89	1.55-5.40	0.001
Negative*	-	-	-	-	-	-
English Registries						
Positive	3.22	1.34-7.78	0.009	2.19	0.82-5.82	0.117
Negative*	-	-	-	-	-	-
Sample Size						
>=100	2.09	1.19-3.67	0.010	2.04	1.11-3.72	0.021
<100*	-	-	-	-	-	-
Number of Centers						
Single-center	1.85	1.01-3.41	0.049	1.56	0.80-3.05	0.196
Multi-center*	-	-	-	-	-	-
Funding						
Non-Industry	1.99	1.06-3.75	0.033	1.29	0.63-2.67	0.483
Industry*	-	-	-	-	-	-
Registration Type						
Retrospective	1.43	0.85-2.40	0.174	1.47	0.84-2.56	0.174
Prospective*	-	-	-	-	-	-
Design						
Superiority	1.17	0.36-3.80	0.797	1.30	0.35-4.78	0.698
Equivalence or Non-inferiority*	-	-	-	-	-	-

*Reference group

RR: Relative Risk; CI: Confidence Interval; ChiCTR: Chinese Clinical Trial Registry.

Figure 1 Identifying Published CS-RCTs



Chapter 3

Duplicate Patterns and Duplicate publication Bias among Randomized Controlled Trials

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Abstract

Importance The impact of duplicate publications may be complicated by the language of publications.

Objective To develop the duplicate patterns and estimate duplicate publication bias modified by the language of publications.

Design Retrospective cohort study.

Settings Trial registries and bibliographic databases.

Participants RCTs conducted in mainland China between 2008 and 2014. RCTs were retrieved from trial registries and their Journal articles were identified from bibliographic databases until August 2019. Journal articles were classified as the main article (with the largest sample size) and duplicates (no reference to the main article). Cross-language duplicates referred to those published in a different language from the main articles.

Four duplicate patterns were developed: (1) unreferenced subgroup analysis (an article fails to disclose itself as a subgroup analysis or reference its main article); (2) unreferenced republication (an article fails to disclose itself as a replicate of the main article or reference it); (3) unreferenced interim analysis (an article fails to disclose itself as an interim analysis or be referenced by its main article); (4) partial duplicate (an article fails to disclose its sharing a subset of participants with other articles or reference them).

Exposure The findings of RCTs (Positive vs. Negative).

Main Outcomes and Measures The main outcome was an RCT having subsequent duplicates. We hypothesized that the main article of an RCT with positive findings was more likely to have subsequent duplicate(s) than those with negative findings.

Results Among 470 RCTs published as journal article(s), 55 (11.7%) had 75 duplicates, of which 53 (70.7%) were cross-language duplicates. 33 (44.0%), 25 (33.3%), 15 (20.0%), and 2 (2.7%) of 75 duplicates were unreferenced republications, unreferenced subgroup analyses, unreferenced interim analyses, and partial duplicates, respectively.

When the main article of an RCT was published in Chinese, those with positive findings were 2.48 (95%CI: 1.08 – 5.71) times more likely to have subsequent duplicates than those with negative findings.

Conclusion and Relevance Most duplicates of RCTs from China were cross-language duplicates and unreferenced republications of the main article. Duplicate publication bias exists when the main articles were published in Chinese, posing a threat to readers, journals, and evidence synthesis when RCTs from China are involved.

Introduction

A duplicate publication (referred to as a duplicate) '*overlaps substantially with one already published, without clear, visible reference to the previous publication*'.[1] Duplicates waste resources, breach copyright, undermine the integrity of research, and distort evidence if inadvertently included in systematic reviews.[2-4]

When disseminating vital messages, secondary publications across languages can be justified, or even recommended, to maximize audience.[1] Such secondary publications should appropriately disclose the relationship to the main publication to avoid being treated as an independent study, i.e., a duplicate.[1]

Duplicates are prevalent in the health-related literature;[5-10] however, it remains challenging for readers, editors and meta-analysts to detect duplicates, especially when the authorship, design, and results of duplicates deviate from the main publication.[11] Moreover, duplicates may be concealed by language barriers thereby becoming even more challenging to be discovered. For example, it is not expected for English-speaking peer reviewers and editors to detect a duplicate originating from a non-English main publication.

Few studies have been dedicated to assessing the interaction between duplicates and publication language. It is unclear how often the cross-language duplicates occur or what role language plays in producing duplicates and subsequently biasing evidence syntheses. In our study we selected RCTs from mainland China as an example, because there are several factors

which facilitate our study: (1) the biomedical research community is witnessing a proliferation of RCTs in China;[12,13] (2) most Chinese literature is not indexed in English bibliographic databases, while a shift towards publishing RCTs from China in English has not been observed;[14,15] (3) the coverage of the Chinese literature by English bibliographic databases has been gradually increasing;[16,17] and (4) the Chinese literature and bibliographic databases have been increasingly recognized by the evidence synthesis community.[18] The aims of this study were to estimate prevalence and detect patterns of duplicates among RCTs from mainland China, and to evaluate the existence of duplicate publication bias with a focus on the interaction between duplication and language.

Methods

In this study, we retrieved eligible RCTs from trial registries, identified the corresponding journal articles from bibliographic databases, developed patterns and evaluated bias regarding duplicate publications. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[19] The study was not subject to institutional review board approval because all the data were open-source and no participant was involved.

Identify Eligible RCTs from Trial Registries and Bibliographic Databases

Our study sample comprised of RCTs sponsored by organizations located in mainland China. The process to retrieve registration records from trial registries and identify corresponding journal articles from bibliographic databases has been described previously.[20] Eligible RCT were defined as those that evaluated the efficacy and/or safety of drugs and were conducted between January 1, 2008 and December 31, 2014. A substance was considered a drug if regulated by the United States Food and Drug Administration and/or the European Medicine Agency. We excluded bioequivalence studies, pharmacokinetics studies, and RCTs with

missing information on eligibility of participants, study period, experimental drug(s), principal investigators, or sponsor.

Only journal articles originating from eligible RCTs were included. The search strategy and terms updated from previous studies,[21-23] list of bibliographic databases,[24] and criteria to match journal articles with registry records are described in Supplements 1-4. Two authors (YJ and DH) independently searched bibliographic databases and identified matching PDFs of eligible RCTs. Discrepancies were discussed and resolved with a third author (JW).

Identify the Main Article and Duplicates

All the journal articles produced from one RCT formed a cluster.[11] We defined the main article as the one with the largest sample size and the longest follow-up. If multiple articles existed with the same sample size and follow-up period, the one submitted earliest to a journal was considered the main article. A duplicate was operationally defined as an article that had at least one duplicated outcome but failed to disclose its relationship with, or reference to, or be referenced by the main article.

In this study we focused on duplicates that might distort evidence, so duplicates were considered only in terms of outcomes regardless of the background, method, or discussion section of the article. We dissected outcomes into five elements, i.e., domain (e.g., systolic blood pressure), specific measurement (e.g., a device at sitting position), specific metric (e.g., change from baseline), the method of aggregation (e.g., mean/median), and time-points.[25] An outcome was considered duplicated if it had the identical domain, specific measurement, and time-point with an outcome in the main article, regardless of the specific metric or the method of aggregation. For example, an article was considered a duplicate if it reported the mean of systolic blood pressure while the main article reported the median, as long as the measurement and time-point were consistent.

Duplicate Patterns

We developed four patterns of duplicates based on the progress of recruitment and follow-up of individual RCTs: (1) unreferenced subgroup analyses; (2) unreferenced republications; (3) unreferenced interim analyses; and (4) partial duplicates.

Unreferenced Subgroup Analysis This is defined as an article that fails to disclose itself as a subgroup analysis or reference its main article. Unreferenced subgroup analyses are published following the main articles. We defined three sub-patterns: (i) subgroup of recruiting centers, in which only participants from a subset of recruiting centers are included; (ii) subgroup of treatment groups, in which only participants from a subset of treatment groups are included; and (iii) subgroup of participants' characteristics, in which only participants with specific characteristics are included, for instance, the main article is on heart failure while the unreferenced subgroup analysis is on heart failure and diabetes.

Unreferenced Republication This is defined as an article that fails to disclose itself as a replicate of the main article, i.e., reports identical participants and follow-up period with the main article, or references the main article. Unreferenced republications are published following the main articles.

Unreferenced Interim Analysis This is defined as an article that fails to disclose itself as an interim analysis or be referenced by the main article published subsequently. We defined three sub-patterns: (i) interim report of recruitment, which reports an interim analysis on a subset of participants before recruitment is complete, usually the participants recruited in the early stage; (ii) interim report of follow-up, which reports an interim analysis on all the participants but before the follow-up is complete, usually on short-term outcomes; and (iii) interim report of both recruitment and follow-up, i.e., an interim analysis on a subset of participants before recruitment and follow-up are complete.

Partial Duplicate A partial duplicate is an article that contains a portion of unique participants while sharing a portion of participants, e.g., a subset of recruiting centers or recruiting period, with a main article which is not referenced. Partial duplicates are published following the main articles.

We also classified duplicates into cross-language duplicates and same-language duplicates. Cross-language duplicates refer to those published in a different language from the main articles, i.e., the main article is published in Chinese and the duplicate in English, or vice versa. Same-language duplicates refer to those published in the same language as the main articles, i.e., the main article and the duplicate are both published in Chinese or English.

Duplicate Publication Bias

We hypothesized that a main article with positive findings was more likely to have subsequent duplicate(s) than those with negative findings.

Exposure An article was classified as positive or negative according to its primary outcome. If multiple primary outcomes were reported, the first one reported in the results section was selected. If no primary outcome was defined, we selected the primary outcome based on the following hierarchical order: the first outcome used in the sample size calculation, the first outcome defined in the study objectives, or the first outcome reported in the results section.[26] When the primary outcome was measured at multiple time points, we considered the last time point in the analysis.

We defined positive findings as favoring the study hypothesis with statistical significance. For example, a superiority trial was positive when the experimental drug was significantly superior over the comparator. We defined negative findings as not statistically significant or contradictory to the study hypothesis.

Outcome A main article had duplicate(s) when at least one unreferenced subgroup analysis, one unreferenced republication, or one partial duplicate was identified in the same cluster.

Effect Modifier We hypothesized that the language of the main article was a possible effect modifier, i.e., the association between the study findings and having subsequent duplicate(s) might vary by the language of the main article.

Measurements of Associations Duplicate Publication Bias was estimated by the relative risk (RR). An RR larger than one indicates that a main article was more likely to have subsequent duplicate(s) when the findings were positive. RRs were estimated using log binomial models with four covariates: language of the first journal article (Chinese versus English), sample size (<100 versus ≥100), funding source (industry versus non-industry), and number of recruiting centers (single versus multiple).[27-29] An RCT was defined as funded by industry if at least one funder was from industry. An interaction term was included in the model to account for the language of the main article as an effect modifier. Statistical significance was defined as a p value less than 0.05 for the main effect and 0.1 for interactions. SAS® 9.4 was used for data management and analysis.

Results

In total, 891 eligible RCTs were identified from five registries. Through August 2019, 470 trial results had been published as journal article(s). 75 duplicates were identified from 55 RCTs (11.7%), of which 47 (63.5%) were in Chinese (Figure 1). The majority (45/55, 81.8%) of clusters only had 1 duplicate, while 10 had more than one duplicates (range: 1 to 6).

53 (70.7%) duplicates crossed language, including 20 (26.7%) in English (while the main article was in Chinese) and 33 (44.0%) in Chinese (while the main article was in English). 22 (29.3%)

duplicates were in the same language as the main articles, including 15 (20.0%) in Chinese and 7 (9.3%) in English.

The characteristics of RCTs having duplicate(s) were generally similar to RCTs without duplicates. Among 55 RCTs having duplicate(s), 10 (18.8%) were sponsored by industry (as opposed to non-industry), 25 (47.2%) recruited fewer than 100 participants, 13 (24.5%) were conducted at one recruiting center only, and 38 (71.7%) reported positive findings. Among 415 RCTs without duplicates, 83 (19.9%) were sponsored by industry, 162 (38.9%) recruited fewer than 100 participants, and 135 (32.4%) were conducted at one recruiting center. The nature of findings was not determined for 2 RCTs without duplicates in which no between-group comparison was reported and were excluded from the analysis on bias. In the remaining 413 RCTs without duplicates, 292 (70.4%) reported positive findings.

Duplicate Patterns

The duplicate patterns are shown in Table 1.

The most prevalent pattern was unreferenced republication. Thirty-three (44.0%) of 75 duplicates fit this pattern, including all 4,044 participants reported in the main articles. Twenty-five (75.8%) duplicates crossed language, including 15 (45.5%) in English (while the main article was in Chinese) and 10 (30.3%) in Chinese (while the main article was in English).

Twenty-five (33.3%) duplicates were unreferenced subgroup analyses, of which 7 (28.0%) were subgroups of centers, 4 (16.0%) were subgroups of treatment groups, 4 (16.0%) were subgroups of participants' characteristics, 2 (8.0%) were subgroups of both centers and participants' characteristics, and 8 (32%) were unclear owing to lack of sufficient information. The 25 unreferenced subgroup analyses included 2,193 (66.6%) of 3,295 participants reported in the main articles. Fifteen (60.0%) duplicates crossed language, including 11 (44.0%) in

Chinese (while the main article was in English) and 4 (16.0%) in English (while the main article was in Chinese).

Fifteen (20.0%) of 75 duplicates were unreferenced interim analyses, of which 13 were analyses of recruitment, 2 were analyses of follow-up, and 1 was an analysis of a mixture of recruitment and follow-up. The 15 unreferenced interim analyses included 1,125 (45.6%) of 2,468 participants reported in the main articles. Twelve (80.0%) duplicates crossed language, all of which were in Chinese (while the main articles were in English).

There were 2 partial duplicates (2.7%), of which one crossed language and the other was the same language as the main article.

Duplicate Publication Bias

We did not find evidence supporting the language of the main article as an effect modifier (χ^2=1.60, P=0.21). After adjusting for covariates, when published in Chinese, the main articles with positive findings were 2.48 (95% CI: 1.08 to 5.71) times more likely to have subsequent duplicate(s) than RCTs with negative findings. There was no evidence supporting a similar bias when the main articles were published in English (RR=0.99, 95%CI: 0.31 to 3.13). The main articles published in Chinese were 7.68 (95%CI: 3.72 to 15.87) times more likely to have subsequent duplicate(s) than those published in English. None of other covariates reached statistical significance (Table 2).

Discussion

Our study revealed that duplicates continued to haunt the medical literature, especially those published in different languages which were challenging to detect. It is unclear how likely the

occurrence of duplicates is due to lack of awareness: it is possible that some researchers may produce duplicates unaware of the inappropriateness, while others may do so deliberately.

Aside from research integrity and legal considerations, the presence of duplicates carries the potential to distort evidence by double-counting trials results in systematic reviews.[3,4] Currently there is a deep gap between English and Chinese literature, i.e., most Chinese RCTs are published in Chinese and only indexed in Chinese bibliographic databases, and very few Chinese journals are covered by major English bibliographic databases.[14,16] Meanwhile, systematic reviews, which should bridge the language gap, nearly always fail to search Chinese bibliographic databases and subsequently do not include RCTs published in Chinese.[30] Under such circumstances, the cross-language duplicates, especially when the main articles are published in Chinese while the duplicates are in English journals, raise serious concerns. An English duplicate is more accessible to most reviewers than the Chinese main article, but it is possible that the duplicate is only a subset of participants with positive findings or with larger effect sizes. Although this type was only present in 5% of all duplicates in our sample, reviewers should be vigilant considering the sheer quantity of RCTs being conducted in China.

On the other hand, simply excluding the Chinese literature may lead to other negative consequences, for example, missing relevant RCTs may lead to narrower confidence intervals than if these RCTs were not missing.[14] Moreover, we observed a language bias among RCTs, which means positive findings stand a higher chance to then be published in English than negative findings; excluding the Chinese literature may increase the risk of overestimating treatment effects.[20] Meanwhile, the coverage of Chinese journals by major English bibliographic databases has been increasing gradually, while more and more systematic reviews on some specific topics have recently started to include Chinese bibliographic databases to reduce bias.[18] The trend of increasing overlap between English and Chinese literature exemplifies the possibility of distorting evidence by including duplicates, because all the patterns could possibly

be included in systematic reviews. Theoretically, unreferenced republications would be the greatest threat as they carry the weight of entire trials. However, as their study participants and results are typically identical to the main articles, it may not be difficult for a meticulous reviewer to detect them. On the other hand, unreferenced subgroup analyses and unreferenced interim analyses can differ tremendously from the main articles, which may be more challenging for reviewers and editors to detect.

Although we did not find evidence that the language of the main article was an effect modifier, the association between the nature of findings of the main articles and the possibility of having subsequent duplicate(s) was only statistically significant when they were published in Chinese, a phenomenon that might be explained by the desire to publish in English journals with higher impact factors and reputation. This also implies that the language of publication may have the potential to modify the duplicate publication bias, and that the negative result in our study may be owing to a small sample size.

In our study, we could not determine the duplication status of some articles owing to a lack of key information or inconsistencies between trial registries and published journal articles.[31-33] Improving the data quality of trial registries and the reporting quality of journal articles could enable reviewers to capture duplicates in a more efficient manner.

There are several limitations of this study. First, the sample size of RCTs in the study was limited. A larger sample size would enable us to better quantify the effect of language on bias. Second, we applied strict rules with high specificity to identify duplicates at the cost of sensitivity and consequently we may have missed some duplicates – especially those which are substantially inconsistent with the main articles, or lacking information for classification. Thus, the actual prevalence of duplicates among RCTs may be much higher than our estimate and there may be patterns of duplication that we failed to identify. Third, because less than 15% of RCTs were registered, RCTs in trial registries may not be representative of all RCTs.[34] We are

thus reluctant to extrapolate our conclusion to all the RCTs. Fourth, although we found evidence supporting the existence of duplicate publication bias, further study is needed to determine how much duplicates, especially cross-language duplicates, affect the conclusions of individual systematic reviews. Finally, we only selected Chinese RCTs as our study sample and the duplicate prevalence, patterns, and bias may vary in other languages. For example, in Germany, there has been a major trend towards publishing clinical trials in English;[15] as a result, cross-language duplicates may subsequently disappear. Nonetheless, we believe our study is informative for future research on RCTs in other languages.

Conclusion

Most duplicates were cross-language duplicates and unreferenced republications of the main article. Duplicate publication bias exists when the main articles were published in Chinese while the duplicates in English, posing a threat to readers, journals, and evidence synthesis when RCTs from China are involved.

Table 1 Patterns of Duplicates

Pattern	Sub-Pattern	Cross Language			Same Language			Total
		English*	Chinese**	Total	Chinese	English	Total	
Unreferenced Interim Analysis	Interim Reported of Recruitment	0	9	**9**	2	1	**3**	**12**
	Interim Reported of Follow-up	0	2	**2**	0	0	**0**	**2**
	Interim Reported of Recruitment and Follow-up	0	1	**1**	0	0	**0**	**1**
	Total	**0**	**12**	**12**	**2**	**1**	**3**	**15 (20.0%)**
Unreferenced Republication	-	**15**	**10**	**25**	**6**	**2**	**8**	**33 (44.0%)**
Unreferenced Subgroup Analysis	Subgroup of Centers	2	1	**3**	4	0	**4**	**7**
	Subgroup of Treatment Groups	0	3	**3**	1	0	**1**	**4**
	Subgroup of Participants' Characteristics	0	2	**2**	0	2	**2**	**4**
	Subgroup of Centers and Participants' Characteristics	0	2	**2**	0	0	**0**	**2**
	Unclear	2	3	**5**	2	1	**3**	**8**
	Total	**4**	**11**	**15**	**7**	**3**	**10**	**25 (33.3%)**
Partial Duplicate	-	**1**	**0**	**1**	**0**	**1**	**1**	**2 (2.7%)**
Total	**-**	**20 (26.7%)**	**33 (44.0%)**	**53 (70.7%)**	**15 (20.0%)**	**7 (9.3)**	**22 (29.3%)**	**75 (100.0%)**

*Duplicate are published in English, while main articles are published in Chinese.

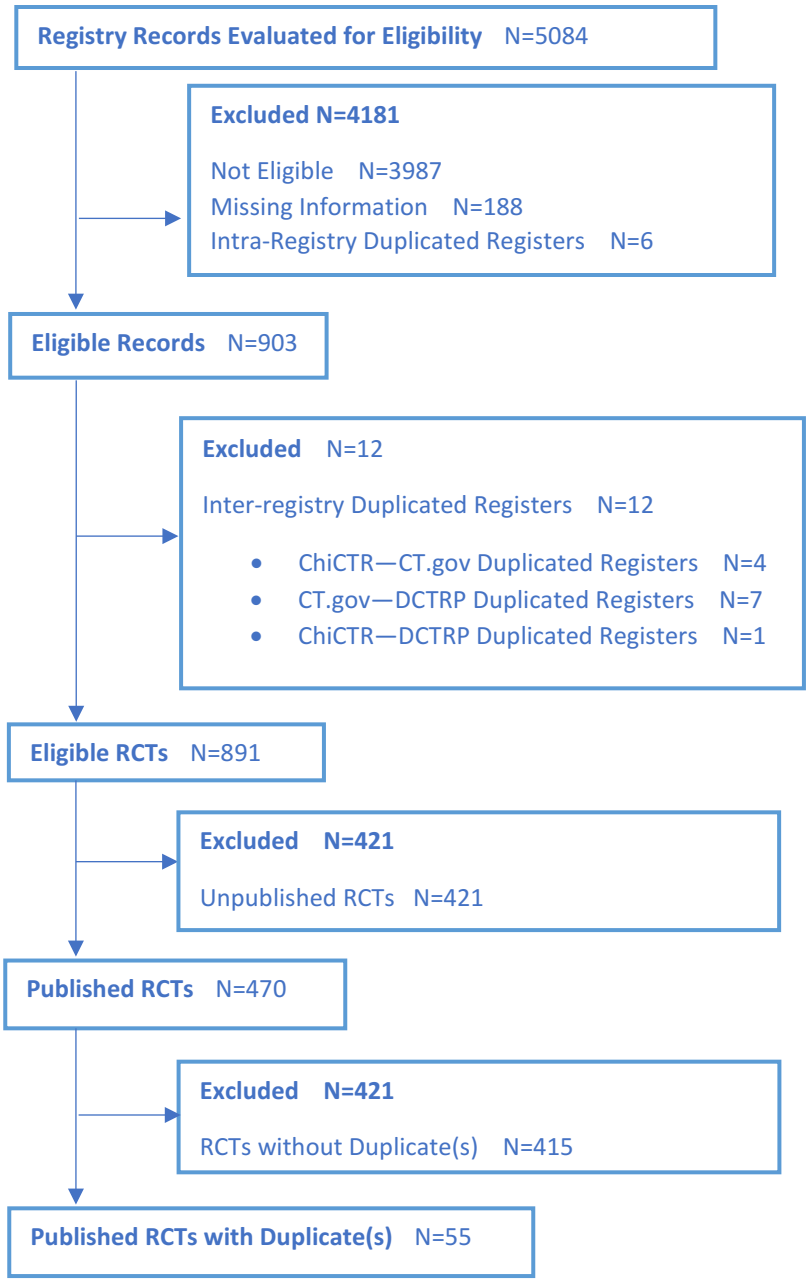
*Duplicate are published in Chinese, while main articles are published in English.

Table 2 Factors Associated with Duplicate Publication Bias

Factor	Comparison	RR	95% CI		P Values
			Lower Limit	Upper Limit	
Nature of Findings of the Main Article					
the Main Article is in Chinese	Positive vs. Negative	2.48	1.08	5.71	0.03
the Main Article is in English	Positive vs. Negative	0.99	0.31	3.13	0.99
Language of the Main Article	Chinese vs. English	8.03	3.91	16.46	<0.01
Sample Size	⩾100 vs. <100	1.07	0.54	2.13	0.85
Funding	Non-Industry vs. Industry	1.39	0.59	3.26	0.45
Number of Recruiting Centers	Single Center vs. Multiple Centers	1.58	0.71	3.50	0.26

RR: Relative Risk

Figure 1 Selection of RCTs with Duplicate(s)



Conclusion

Summary of Findings and Implications

This dissertation was among the first attempts to evaluate reporting bias among RCTs from mainland China. Chapter 1 was the first study to evaluate the switching of registered primary outcomes. Chapter 2 was the first study to evaluate language bias between Chinese and English literature and indexing bias between English and Chinese bibliographic databases. Chapter 3 was the first study to evaluate duplicate publication bias. We found evidence supporting all three types of reporting bias.

Findings of Chapter 1

Chapter 1 focused on the switching of pre-specified primary outcomes of RCTs. We found evidence supporting that registered primary outcomes with negative findings were more likely to be downgraded to secondary outcomes in the subsequent journal articles than those with positive findings. This association between the switching of primary outcomes and the nature of findings was consistent across trial registries (bilingual registry vs. English registries), but was modified by the timing of registration (prospectively registered vs. retrospectively registered before trial completion vs. retrospectively registered after trial completion). The strongest association was observed when RCTs were retrospectively registered before trial completion.

Implications of Chapter 1

The switching of primary outcomes would not distort evidence synthesized by systematic reviews should all outcomes are appropriately disclosed. However, researchers may selectively report outcomes with positive findings, a phenomenon termed outcome reporting bias;[35] the pre-specified primary outcomes with negative findings are at risk to be downgraded to secondary outcomes and omitted from publications, which would result in overestimated evidence.

On the other hand, the switching of primary outcomes may inappropriately underline positive findings and bias the interpretation of individual RCTs. Primary outcomes of clinical trials are carefully selected at the design stage which are deemed most important and relevant to the research question, of which the probability of false positivity or false negativity are controlled by appropriate sample size and statistical testing.[36] On the contrary, secondary outcomes with positive findings bear higher probability of false positivity.[37] Downgrading a negative pre-specified primary outcome to be secondary in the publication while upgrading a positive pre-specified secondary outcome to be primary in the publication grants the secondary outcome the equivalent importance and credibility of a primary outcome. The interpretation of the RCT based on the newly introduced primary outcome, which is very likely to be false positive, is at high risk of bias.

The switching of primary outcome can flip the interpretation of an RCT from 'failure' to 'success' among health care providers, researchers, and journal editors. When systematic reviews are not available, the evaluation of health interventions by stakeholders may rely on individual RCTs. It is possible to adopt a health intervention by stakeholders that is of little therapeutic value to patients when primary outcome switching occurs. In addition, switching of pre-specified primary outcomes among pivotal trials may lead to marketing license of health interventions granted by legal authorities that is of little therapeutic value to patients.

Recommendations of Chapter 1

The switching of primary outcomes can be detected by comparing publications with protocols, which unfortunately are not always available to the public. With key items of protocols, trial registries remain a powerful alternative for researchers to detect and evaluate the switching of primary outcomes. However, to date less than 15% of RCTs from mainland China have been registered, restricting the role of trial registries.[38] This chapter advocates prospective registration of all RCTs from mainland China to facilitate detection of primary outcome switching, the first

step to reduce its occurrence in the future. In addition, reviewers of manuscripts of RCTs are recommended to compare the manuscripts with registries to detect any switching of primary outcomes; authors of manuscripts should be required to explain any identified discrepancy.

Findings of Chapter 2

Chapter 2 focused on the language bias and indexing bias. We found evidence supporting that RCTs with positive findings were more likely to be published in English and indexed in English bibliographic databases than those with negative findings. The direction of associations (between the nature of findings and the language of the subsequent journal articles, between the nature of findings and the language of bibliographic databases where the journal articles were indexed) were consistent across registries, although the magnitude of associations were larger among RCTs retrieved from bilingual registry than those from English registries.

Implications of Chapter 2

English-speaking investigators, who fail to consider Chinese literature when searching English bibliographic databases, are more likely to include positive findings in systematic reviews to overestimate treatment effect when research from mainland China is involved. Removing language restrictions to include Chinese literature indexed in English bibliographic databases can only capture a small fraction of Chinese journals, therefore, to reduce the impact of language bias to a very limited extent owing to indexing bias. Only by searching Chinese bibliographic databases to include all Chinese literature can researchers further eliminate the impact of both language bias and indexing bias on systematic reviews.

Language bias and indexing bias unproportionally expose positive findings to researchers synthesizing evidence, which may lead to overestimate of treatment effect. Traditionally Chinese literature has been overlooked by researchers in English-speaking countries except for

certain treatments originated from China.[39] This chapter rings the alarm for possible bias introduced into systematic reviews by overlooking Chinese literature.

Recommendations of Chapter 2

There are several ways to possibly reduce the impact of language bias and/or indexing bias. First, there has been a prolonged discussion about the necessity of including Chinese bibliographic databases in systematic reviews. The reporting and conducting quality of RCTs in Chinese bibliographic databases is allegedly lower than their English counterparts.[40] Some English-speaking researchers argue it may not be worth the time and resources to comprehensively search bibliographic databases in another language. Although it is still at the discretion of individual researchers to value Chinese bibliographic databases, Chapter 2 tips the balance towards including them in systematic reviews.

Second, the comprehensive registration of RCTs from mainland China can help researchers identify all RCTs regardless of where they are published or indexed. Targeting the RCTs from registries may reduce the workload of researchers to a substantial extent. Again, it is urgent to improve the registration of RCTs from mainland China.

Third, it is possible to reduce the impact of indexing bias by increasing the coverage of Chinese journals by major English bibliographic databases, such as PubMed and Embase, therefore researchers would be able to identify all relevant Chinese literature by removing language restriction when search English bibliographic databases. However, it is challenging to include all Chinese journals owing to their suboptimal quality.[41]

Findings of Chapter 3

Chapter 3 focused on the patterns of duplicates and duplicate publication bias. We found evidence supporting that more than 10% of RCTs from mainland China had at least one duplicate. The duplicates could be classified as four patterns: (1) unreferenced subgroup

analysis (an article that reports a subgroup analysis of an RCTs but fails to reference its main article.); (2) unreferenced republication of the main article (an article that reports all the participants with complete follow-up in an RCT but fails to reference its main article); (3) unreferenced interim analysis (an article that reports an interim analysis of an RCT but is not referenced by the main article published subsequently); and (4) partial duplicate (shared a subset of participants with other articles but no reference). Most duplicates were unreferenced republication of the main articles and published in a different language from the main articles. When the main articles were published in Chinese, RCTs with positive findings were more likely to have subsequent duplicates than those with negative findings. This duplicate publication bias was not supported when the main articles were published in English.

Implications of Chapter 3

Duplicates may be challenging to detect, especially when the authorship, design and results of duplicates are inconsistent with the main articles. In non-English speaking countries, the occurrence of duplicates may be further complicated by the language barrier. It is challenging for English-speaking researchers, journal editors, and reviewers to detect an English duplicate when the main article is published in Chinese.

Producing duplicates constitutes plagiarism and violates copyright. The resume of researchers may be inappropriately enriched by including duplicates. Moreover, Duplicate publication bias may result in more positive findings from duplicates being inadvertently included in systematic reviews to overestimate treatment effects. Although we reported four patterns of duplicates to shed a light on how duplicates occurred, it is noteworthy that there may be more patterns that are too complicated or obscure to be detected by researchers solely based on publications.[11]

Recommendations of Chapter 3

We recommend academic journals to update the instruction for authors to highlight that publishing original data secondarily in another language without referencing the primary publication is not acceptable. Researchers conducting systematic reviews should be alerted to the possible existence of cross-language duplicates and actively search for them if necessary, especially for the patterns detected in this dissertation.

The importance of trial registration is highlighted again by Chapter 3. It would be much easier for researchers to detect duplicates if all trial-related publications provide registration identity, an action that should be taken by all academic journals. In addition, intentionally produced duplicates are considered scientific misconduct.[42] By developing appropriate regulations, the government may establish watchdog to actively monitor and take legal actions against possible duplicates. Such legal actions may also be considered by academic journal of which copyright is violated.

All three types of reporting bias favored positive findings, posing a risk of overestimating treatment effects. Researchers synthesizing evidence, journal editors, and policy makers should be aware of those biases. Imminent actions, such as strengthening trial registration, including Chinese literature and Chinese bibliographic databases in reviews, and updating the author instructions of journals should be considered in the future.

Future Directions

We suggest eight pathways for future studies.

First, we only evaluated three types of reporting bias among RCTs from mainland China. More studies are needed to evaluate other types of reporting bias, such as publication bias, outcome

reporting bias, time lag time, citation bias, etc. For example, there have been concerns over the disproportionate abundance of positive findings from RCTs from mainland China. One possible explanation may be an alarming publication bias, therefore positive findings are more likely to be published. Such concerns warrant future research.

Second, we only included RCTs from trial registries. Because only a few RCTs from mainland China are registered, it is unclear whether the selected RCTs in this dissertation can be representative of all RCTs from mainland China, therefore any direct extrapolation of the conclusions to other settings may not be appropriate. More studies on representative samples are recommended to assess reporting bias in the future, for example, RCTs approved by ethics committees of research hospitals or funded by government agencies.

Third, we did not assess the impact of the reporting bias, including language bias and duplicate publication bias, on individual systematic reviews. Although we found evidence supporting the existence of reporting bias on the level of the clinical trial community, it was unclear whether and how much reporting bias would distort evidence synthesized by individual systematic reviews. For example, for specific systematic reviews on research topics that did not involve research from mainland China, language bias should not be a concern. How many and how much of systematic reviews could be affected by those types of reporting bias remain unclear and warrant future research.

Fourth, the sample size of this dissertation was limited. It was not feasible to evaluate the trend of reporting bias over time. For example, are those types of reporting bias changing over time? Is the prevalence of duplicates increasing? Are there new patterns of duplicates? It is necessary to trace the change of reporting bias in the future.

Fifth, we only evaluated one or two possible effect modifiers in each chapter. There may be more interesting confounders or effect modifiers to explore, which warrant a larger sample size.

For example, some RCTs having more than three registered primary outcomes may be different from those with a single registered primary outcome in terms of primary outcome switching; RCTs published in Chinese are less likely to specify primary outcomes than those published in English, which may have impact on reporting bias.

Sixth, the structure and function of Chinese bibliographic databases should be appropriately upgraded. The major Chinese bibliographic databases are not use-friendly and can only support systematic reviews with limited scope. For example, most Chinese bibliographic databases only allow users to export 50 records at one time, which could be rather cumbersome for researchers conducting systematic reviews covering thousands of records. Another major challenge is that none of the Chinese bibliographic databases provide legitimate control vocabulary. Although the Medical Subject Headings (MeSH) developed by the National Library of Medicine to index literature has been translated to Chinese, to date most Chinese literature has not been appropriately indexed by the Chinese bibliographic databases and linked to the Chinese MeSH terms, therefore reviewers could not retrieve records correctly by searching Chinese MeSH terms.

Seventh, although we recommended including Chinese literature and Chinese bibliographic databases in systematic reviews, to date there has been no RCT filter available on Chinese literature. It is urgent to develop RCT filters with varying levels of sensitivity and specificity (e.g., maximum sensitivity, balanced sensitivity and specificity, and maximum specificity) to facilitate retrieval of RCTs from Chinese bibliographic databases.

Eighth, the impact of reporting bias may vary substantially across countries. In this dissertation we only evaluated three types of reporting bias among RCTs from mainland China. Owing to different academic systems and cultures, the significance of reporting bias is expected to be varying. It is necessary to evaluate reporting bias among RCTs from other non-English speaking countries, especially developing countries with rapidly changing situation.

Summary

This dissertation found evidence supporting three types of reporting bias among RCTs from China, including primary outcome switching, language bias/indexing bias, and duplicate publication bias. Registered primary outcomes with negative findings are more likely to be downgraded to secondary outcomes in the subsequent journal articles than those with positive findings; RCTs with positive findings are more likely to be published in English and indexed in English bibliographic databases; RCTs with positive findings are more likely to have subsequent duplicates than those with negative findings. Future research is needed to explore more types of reporting bias among RCTs from mainland China and evaluate their impact on individual systematic reviews.

Appendices

Appendix A: Supplementary Materials for Chapter 1

Supplement 1 Search Strategies

Strategy 1	Single-Center and Multi-Center RCTs	Registration Number
Strategy 2	Single-Center and Multi-Center RCTs	PI's Name AND PI's Affiliation AND (Disease OR Drug) AND Study End Date
Strategy 3	Multi-Center RCTs	Recruitment Facilities AND Disease AND Drug AND Study End Date

PI: Principle Investigator; RCT: Randomized Controlled Trials.

Supplement 2 Search Terms

Database	Identifier	Source of Subjects	Source of Keywords
English	Disease	MeSH Emtree	Registry records PubMed entry terms Embase synonyms
	Drug	MeSH Emtree	Registry records PubMed entry terms Embase synonyms
Chinese	Disease	MeSH (Chinese version)	Registry records ICD-10 (Chinese version) ICD-9 (Chinese version) Three doctors from PUMC
	Drug	MeSH (Chinese version)	Registry records China FDA website for drug trade names and compound names Three pharmacists from PUMC

MeSH: Medical Subject Headings; Emtree: Embase Subject Headings; ICD-9: The International Classification of Diseases, Ninth Revision; ICD-10: The International Classification of Diseases, Tenth Revision; PUMC: Peking Union Medical College; China FDA: China Food and Drug Administration

Supplement 3 Method to Match Journal Articles with Registry Records

Criteria
Similar Eligibility Criteria & Interventions, Same Registration Number
Similar Eligibility Criteria & Interventions, Same Ethics Committee Approval Number
Similar Eligibility Criteria & Interventions, Same Funding Identification
Consistent Eligible Criteria & Interventions, Similar Sample Size & Overlapped Study Period
Consistent Eligible Criteria & Interventions, Identical Sample Size
Consistent Eligible Criteria & Interventions, Identical Study Period

Supplement Table 4 Factors Associated with Discrepancy between Registered and Published Primary Outcomes: Sensitivity Analysis 1 (On Outcomes Designated as Primary in Journal Articles)

Factor	Level	Stratum	OR	95%CI	P Value
Nature of Findings	Negative vs. Positive	Prospective Registration	2.44	1.03 – 5.75	0.04
		Retrospective Before Trial Completion	8.29	3.06 – 22.46	<0.01
		Retrospective After Trial Completion	0.77	0.29 – 2.09	0.61
		ChiCTR & Prospective Registration	2.74	1.21 – 6.20	0.02
		ChiCTR & Retrospective Before Trial Completion	9.32	3.22 – 26.94	<0.01
		ChiCTR & Retrospective After Trial Completion	0.87	0.34 – 2.22	0.77
		English Registries & Prospective Registration	2.17	0.63 – 7.51	0.22
		English Registries & Retrospective Before Trial Completion	7.38	2.09 – 26.08	<0.01
		English Registries & Retrospective After Trial Completion	0.69	0.18 – 2.67	0.59
Registry	ChiCTR vs. English Registries		4.20	1.90 – 9.27	<0.01
Timing of Registration	Prospective vs. Retrospective After Trial Completion		0.49	0.21 – 1.16	0.10
	Retrospective Before Trial Completion vs. Retrospective After Trial Completion		0.52	0.23 – 1.20	0.12
Sample Size	>=100 vs. <100		0.64	0.30 – 1.37	0.25
Funding	Non-Industry vs. Industry		1.09	0.41 – 2.93	0.86
Number of Recruiting Centers	Single vs. Multiple		2.96	1.18 – 7.42	0.02

Abbreviations
ChiCTR: Chinese Clinical Trial Registry; OR: Odds Ratio

Supplement Table 5 Factors Associated with Discrepancy between Registered and Published Primary Outcomes: Sensitivity Analysis 2 (Worst-Case Scenario)

Factor	Level	Stratum	OR	95%CI	P Value
Nature of the Findings	Negative vs. Positive	Prospective Registration	1.20	0.58 – 2.51	0.62
		Retrospective Before Trial Completion	3.05	1.33 – 7.01	0.01
		Retrospective After Trial Completion	0.48	0.19 – 1.17	0.10
		ChiCTR & Prospective Registration	1.57	0.80 – 3.09	0.19
		ChiCTR & Retrospective Before Trial Completion	3.99	1.64 – 9.68	<0.01
		ChiCTR & Retrospective After Trial Completion	0.62	0.27 – 1.42	0.26
		English Registries & Prospective Registration	0.92	0.31 – 2.75	0.88
		English Registries & Retrospective Before Trial Completion	2.33	0.79 – 6.89	0.12
		English Registries & Retrospective After Trial Completion	0.36	0.11 – 1.24	0.11
Registry	ChiCTR vs. English Registries		3.74	1.89 – 7.41	<0.01
Timing of Registration	Prospective vs. Retrospective After Trial Completion		0.47	0.22 – 1.00	0.05
	Retrospective Before Trial Completion vs. Retrospective After Trial Completion		0.69	0.34 – 1.40	0.30
Sample Size	>=100 vs. <100		0.66	0.35 – 1.26	0.21
Funding	Non-Industry vs. Industry		1.53	0.65 – 3.60	0.32
Number of Recruiting Centers	Single vs. Multiple		1.96	0.91 – 4.23	0.09

Supplement Table 6 Factors Associated with Discrepancy between Registered and Published Primary Outcomes: Sensitivity Analysis 3 (Best-Case Scenario)

Factor	Level	Stratum	OR	95%CI	P Value
Nature of the Findings	Negative vs. Positive	Prospective Registration	5.00	2.38 – 10.51	<0.01
		Retrospective Before Trial Completion	17.06	6.88 – 42.31	<0.01
		Retrospective After Trial Completion	2.18	0.92 – 5.15	0.08
		ChiCTR & Prospective Registration	4.66	2.29 – 9.46	<0.01
		ChiCTR & Retrospective Before Trial Completion	15.89	6.2 – 40.72	<0.01
		ChiCTR & Retrospective After Trial Completion	2.03	0.9 – 4.56	0.09
		English Registries & Prospective Registration	5.37	1.82 – 15.87	<0.01
		English Registries & Retrospective Before Trial Completion	18.32	5.76 – 58.25	<0.01
		English Registries & Retrospective After Trial Completion	2.34	0.72 – 7.64	0.16
Registry	ChiCTR vs. English Registries		3.70	1.84 – 7.42	<0.01
Timing of Registration	Prospective vs. Retrospective After Trial Completion		0.54	0.25 – 1.15	0.11
	Retrospective Before Trial Completion vs. Retrospective After Trial Completion		0.50	0.24 – 1.04	0.06
Sample Size	>=100 vs. <100		0.65	0.33 – 1.28	0.21
Funding	Non-Industry vs. Industry		1.38	0.57 – 3.39	0.48
Number of Recruiting Centers	Single vs. Multiple		1.91	0.85 – 4.3	0.12

Appendix B: Supplementary Materials for Chapter 2

Supplement 1 Search Strategies

Strategy 1	Single-Center and Multi-Center CS-RCTs	Registration Number
Strategy 2	Single-Center and Multi-Center CS-RCTs	PI's Name AND PI's Affiliation AND (Disease OR Drug) AND Study End Date
Strategy 3	Multi-Center CS-RCTs	Recruitment Facilities AND Disease AND Drug AND Study End Date

PI: Principle Investigator; CS-RCT: Chinese-Sponsored Randomized Controlled Trials.

Supplement 2 Search Terms

Database	Identifier	Source of Subjects	Source of Keywords
English	Disease	MeSH Emtree	Registry records PubMed entry terms Embase synonyms
	Drug	MeSH Emtree	Registry records PubMed entry terms Embase synonyms
Chinese	Disease	MeSH (Chinese version)	Registry records ICD-10 (Chinese version) ICD-9 (Chinese version) Three doctors from PUMC
	Drug	MeSH (Chinese version)	Registry records China FDA website for drug trade names and compound names Three pharmacists from PUMC

MeSH: Medical Subject Headings; Emtree: Embase Subject Headings; ICD-9: The International Classification of Diseases, Ninth Revision; ICD-10: The International Classification of Diseases, Tenth Revision; PUMC: Peking Union Medical College; China FDA: China Food and Drug Administration

Supplement 3 Method to Match Journal Articles with Registry Records

Category	English Articles		Chinese Articles		Total	
	No.	%	No.	%	No.	%
Confirmed Matches						
Similar Eligibility Criteria & Interventions, Same Registration Number	311	84.5	20	19.6	331	70.4
Similar Eligibility Criteria & Interventions, Same Ethics Committee Approval Number	1	0.3	8	7.8	9	1.9
Similar Eligibility Criteria & Interventions, Same Funding Identification	2	0.5	1	1.0	3	0.6
Consistent Eligible Criteria & Interventions, Similar Sample Size & Overlapped Study Period	38	10.3	40	39.2	78	16.6
Consistent Eligible Criteria & Interventions, Identical Sample Size	7	1.9	3	2.9	10	2.1
Consistent Eligible Criteria & Interventions, Identical Study Period	1	0.3	0	0.0	1	0.2
Total	360	97.8	72	70.6	432	91.9
Probable Matches						
Consistent Eligibility Criteria & Interventions Similar Sample Size	7	1.9	16	15.7	23	4.9
Consistent Eligibility Criteria & Interventions Overlapped Study Period	1	0.3	14	13.7	15	3.2
Total	8	2.2	30	27.4	38	8.1
Total	368	100.0	102	100.0	470	100.0

Supplement 4 Characteristics of Published CS-RCTs by Language of Journal Articles

Category	English Articles		Chinese Articles		Total	
	No.	%	No.	%	No.	%
Positivity						
Positive	276	75.41	47	46.1	323	69.0
Negative	90	24.59	55	53.9	145	31.0
Sample Size						
>=100	230	62.5	56	54.9	286	60.9
<100	138	37.5	46	45.1	184	39.1
Number of Centers						
Multi-center	108	29.35	40	39.2	148	31.5
Single-center	260	70.65	62	60.8	322	69.5
Funding						
Industry	63	17.12	30	29.4	93	19.8
Non-Industry	305	82.88	72	70.6	377	80.2
Registration Type						
Prospective	115	31.25	40	39.2	155	33.0
Retrospective	253	68.75	62	60.8	315	67.0
Design						
Superiority	346	94.54	96	94.1	442	94.4
Equivalence or Non-inferiority	20	5.46	6	5.9	26	5.6
Total	368	100.0	102	100.0	470	100.0

Abbreviations

CS-RCTs: Chinese-Sponsored Randomized Controlled Trials.

Supplement 5 Characteristics of Published CS-RCTs by Language of Bibliographic Databases

Category	English Databases		Chinese Databases		Total	
	No.	%	No.	%	No.	%
Positivity						
Positive	285	72.5	38	50.7	323	69.0
Negative	108	27.5	37	49.3	145	31.0
Sample Size						
<100	147	37.2	37	49.3	184	39.2
>=100	248	62.8	38	50.7	286	60.8
Number of Centers						
Multi-center	123	31.1	25	33.3	148	31.5
Single-center	272	68.9	50	66.7	322	68.5
Funding						
Industry	76	19.2	17	22.7	93	19.8
Non-Industry	319	80.8	58	77.3	377	80.2
Registration Type						
Prospective	125	31.7	30	40.0	155	33.0
Retrospective	270	68.3	45	60.0	315	67.0
Design						
Superiority	371	94.4	71	94.7	442	94.4
Equivalence or Non-inferiority	22	5.6	4	5.3	26	5.6
Total	395	100.0	75	100.0	470	100.0

Abbreviations

CS-RCTs: Chinese-Sponsored Randomized Controlled Trials

Appendix C: Supplementary Materials for Chapter 3

Supplement 1 List of Trial Registries and Bibliographic Databases

Trial Registries

Primary Registries Recognized by the World Health Organization

- Australian New Zealand Clinical Trials Registry (ANZCTR)
- Brazilian Clinical Trials Registry (ReBec)
- Chinese Clinical Trial Registry (ChiCTR)
- Clinical Research Information Service (CRiS), Republic of Korea
- Clinical Trials Registry - India (CTRI)
- Cuban Public Registry of Clinical Trials (RPCEC)
- EU Clinical Trials Register (EU-CTR)
- German Clinical Trials Register (DRKS)
- Iranian Registry of Clinical Trials (IRCT)
- ISRCTN
- Japan Primary Registries Network (JPRN)
- Lebanese Clinical Trials Registry (LBCTR)
- Thai Clinical Trials Registry (TCTR)
- The Netherlands National Trial Register (NTR)
- Pan African Clinical Trial Registry (PACTR)
- Peruvian Clinical Trial Registry (REPEC)
- Sri Lanka Clinical Trials Registry (SLCTR)
- ClinicalTrials.gov

Trial Registry by the China Food and Drug Administration

- Drug Clinical Trial Registry Platform

Bibliographic Databases

- PubMed
- Embase
- the Cochrane Central Register of Controlled Trials (CENTRAL)
- the China National Knowledge Infrastructure (CNKI)
- SinoMed
- the VIP information
- the Wanfang Data

Supplement 2 Search Strategies

Strategy 1	Single-Center and Multi-Center CS-RCTs	Registration Number
Strategy 2	Single-Center and Multi-Center CS-RCTs	PI's Name AND PI's Affiliation AND (Disease OR Drug) AND Study End Date
Strategy 3	Multi-Center CS-RCTs	Recruitment Facilities AND Disease AND Drug AND Study End Date

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Supplement 3 Search Terms

Database	Identifier	Source of Subjects	Source of Keywords
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Chinese	Disease	MeSH (Chinese version)	Registry records ICD-10 (Chinese version) ICD-9 (Chinese version) Three doctors from PUMC
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MeSH: Medical Subject Headings; Emtree: Embase Subject Headings; ICD-9: The International Classification of Diseases, Ninth Revision; ICD-10: The International Classification of Diseases, Tenth Revision; PUMC: Peking Union Medical College; China FDA: China Food and Drug Administration.

Supplement 4 Method to Match Journal Articles with Registry Records

Same Name of Experimental Drug and Targeted Disease, Same Registration Number
Same Name of Experimental Drug and Targeted Disease, Same Ethics Committee Approval Number
Same Details of Experimental Drug and Targeted Disease, Overlapped Study Period, Recruiting Centers and Authorship
Same Name of Experimental Drug and Targeted Disease, Consistent Baseline Characteristics with a Match
Same Name of Experimental Drug and Targeted Disease, Consistent Outcomes with a Match

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PUBLICATIONS

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